Chemistry of 2-amino-4-oxo-4*H*-1-benzopyran-3-carboxaldehydes

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Abstract
The review article gives a comprehensive survey of the synthesis and chemistry of 2-amino-4-oxo-4*H*-1-benzopyran-3-carboxaldehydes, covering the literature to March, 2016.

Keywords: 1-Benzopyran-4-ones, Michael additions, Friedländer annulations, intramolecular cycloadditions, rearrangements, metal complex formation

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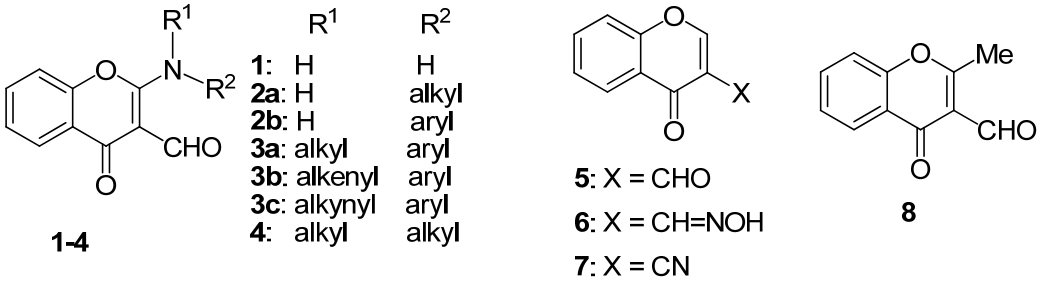
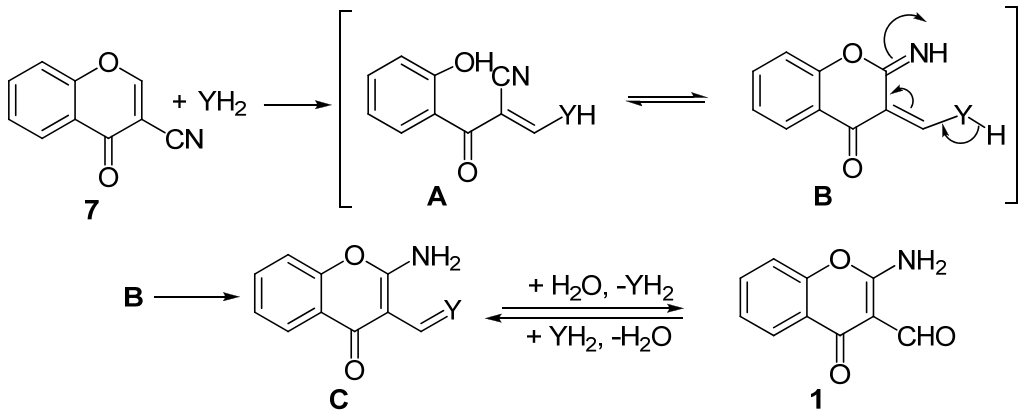
1. Introduction

2-Amino-4-oxo-4*H*-1-benzopyran-3-carboxaldehydes (trivial name: 2-amino-3-formylchromones) (**1**-**4**) like their 2-unsubstituted analogue 3-formylchromone (**5**)[1] possess an activated endocyclic olefinic bond, three electrophilic centres, namely pyran C-2, aldehydic carbon and endocyclic carbonyl carbon, the last named (C-4) being the least electrophilic. Electrophilicity at their amino substituted C-2 is somewhat reduced due to the positive resonance effect of the amino group and compares well to that at C-2 of 3-formyl-2-methylchromone **8**.[2] Again, the chromones **1**-**4** through their amino groups can function as nucleophiles as **8** does through its 2-methyl group in the presence of an appropriate base. The amino-aldehyde **1** in this respect can be regarded as an aza-analogue of the aldehyde **8**. Furthermore nucleofugality of the amino groups, particularly secondary and tertiary ones, in the title chromones while behaving as Michael acceptors towards several nucleophiles, may come to the fore. Because of these functionalities (activated olefinic bond, electrophilicity at three centres, and nucleophilicity and nucleofugality of the amino group), the chemistry of the chromones **1**-**4** is more varied. The present article is a comprehensive survey of the chemistry and applications of the chromones **1**-**4**, and covers the literature to March, 2016. Patented works on the chromones **1**-**4** are not covered, and the biological activity of the compounds **1**-**4** and products obtainable therefrom are less emphasized. Most of the reactions described here for the chromones **1**-**4** generally do not affect any alkyl, alkoxy and halogeno substituents if they are present in the benzene or fused aromatic or heteroaromatic ring in these chromones. Unless specified otherwise, the chromones **2b** (R^1 = H, R^2 = Ph), **3a** (R^1 = Me, R^2 = Ph) and **4** (R^1 = R^2 = Me) are simply written throughout this article as **2**, **3** and **4**, respectively.

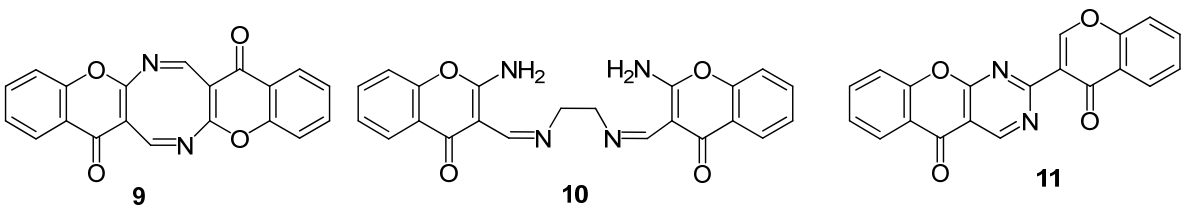


2. Synthesis

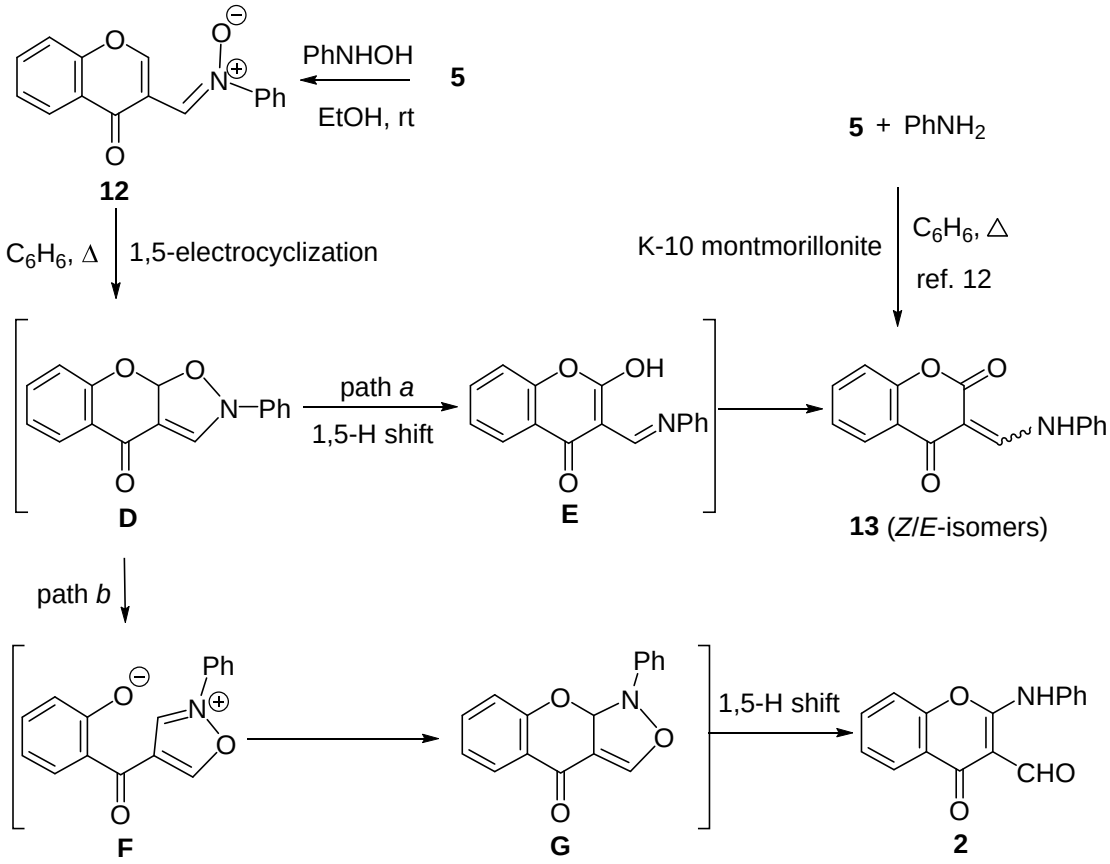
In its reaction with a nucleophile of general form YH_2 the nitrile **7** behaves as a 'chemical equivalent' of the amine **1**, provided the nucleophile undergoes Michael addition to the activated endocyclic olefinic bond of **7** with concomitant pyran ring opening (to **A**) and recyclization (through **B**) to yield **C** obtainable by condensation of **1** with YH_2 (Scheme 1). The compound **C** may, however, undergo further transformation (*vide infra*), depending on the nature of the Y grouping. So the nitrile is indeed the preferred starting material for the synthesis of 2-amino-3-formylchromone **1**. The formation of **1** by treating 3-cyanochromone **7**, derived from the aldehyde **5** *via* the oxime **6**, with an aqueous ethanolic solution (2%) of sodium hydroxide at 70 °C,[3] with a small amount of morpholine in DMF-H_2O at 60°C,[4,5] with ethylenediamine in aqueous ethanol (1:1) under reflux,[6] or by stirring a solution of 3-cyanochromone in CH_2Cl_2 with alumina at ambient temperature[7] has been reported. The aldehyde **1** can also be prepared by warming an ethanolic solution of the aldoxime **6** with aqueous NaOH.[3] Ethylenediamine-induced self-condensation of **6** as well as **7** gives the fused 1,5-diazocine **9** which is hydrolysed in boiling aqueous acetic acid to the amino-aldehyde **1**.[8] Heating the nitrile (1 equiv) with ethylenediamine (0.5 equiv) in ethanol for 10 min is reported to produce the bis-imine **10**, which, depending on the time of reflux in AcOH, affords the amine **1** or the benzopyranopyrimidine **11**.[9] All these methods for the conversion of the nitrile **7** to the aldehyde **1** are fully discussed in a review article.[10]



Scheme 1

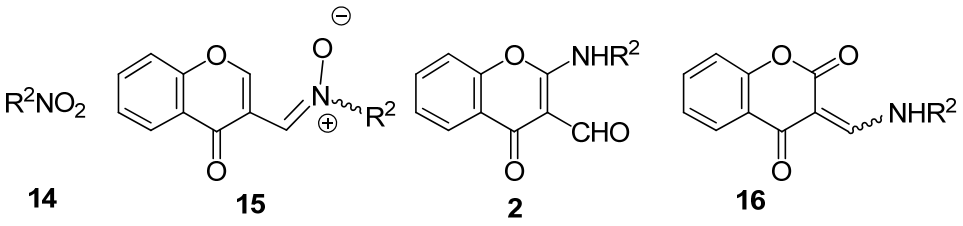


C-(4-Oxo-4*H*-1-benzopyran-3-yl)-*N*-phenylnitrone **12**, obtainable from the aldehyde **5** and phenylhydroxylamine, undergoes facile rearrangement on refluxing in benzene yielding 2-anilino-3-formylchromone **2** (70%) and 3-(phenylaminomethylene)chroman-2,4-dione **13** (*E*/*Z*-mixture, 25%) (Scheme 2).[11] The intermediate **D** arising from an initial 1,5-electrocyclization of the nitrone **12** undergoes a 1,5-H shift giving through **E** the chromandione **13** (path *a*). An alternative rearrangement of **D** involving its conversion to the pyran ring opened intermediate **F** followed by recyclization (→ **G**) and a 1,5-H shift yields the 2-anilinochromone **2** (path *b*). It is pertinent to mention here that a solution of the aldehyde **5** and aniline in benzene containing K-10 montmorillonite on reflux with stirring affords an *E*/*Z*-mixture of **13** in ~45% yield.[12]



Scheme 2

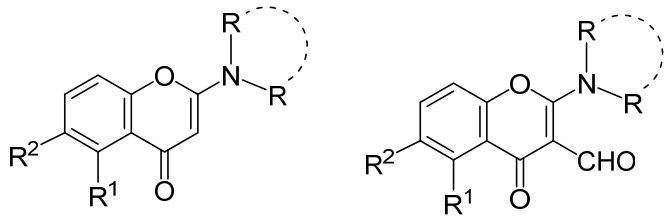
Ghosh and Bandyopadhyay[13] have shown that the rearrangement of the nitrone **15**, prepared by reacting the aldehyde **5** with nitro -alkane or -arene **14** and zinc in EtOH in the presence of AcOH, to either the aldehyde **2** (R^1 = H, R^2 = alkyl or aryl) or/and dione **16**, is a solvent-dependent process. The nitrone **15a** whether refluxed in a protic solvent (MeOH or EtOH) or an aprotic solvent (MeCOMe, MeCN) gives **2a** exclusively. Arylnitrone **15b** fails to rearrange in boiling MeOH but readily rearranges to **2b** when heated under reflux in ethanol or acetonitrile. Both the nitrones **15a**,**b** when stirred in AcOH at room temperature rearrange to **2a,b**. In contrast, each of the nitrones **15** in refluxing toluene or xylene gives the dione **16** (an *E*/*Z*-mixture) as the major product (60-80%), together with the aldehyde **2** (10-20%). It seems clear that a protic solvent has little effect on the rearrangement, but its outcome depends on the polarity of the solvent and also on the reaction temperature.



14 **15** **2** **16**

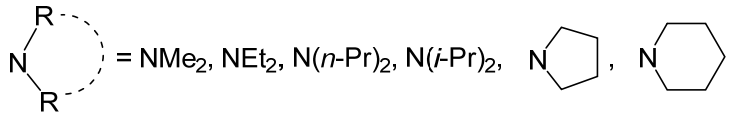
For **2**,**14-16** **a** : R^2 = Me, Et
b : R^2 = Ph, C_6H_4Me-4

A one-pot synthesis of the aminochromone **2** by Zn-aq.NH_4Cl mediated reaction of the aldehyde **5** and nitro compound **14** in THF has been achieved.[14] The reaction mixture of **5** and **14a** when stirred for 7 h at room temperature affords 2-(*N*-alkylamino)chromone **2a** (~45%), $MeNO_2$ additionally producing a small amount of the Knoevenagel condensation product, the 3-(2-nitrovinylchromone). A stirred reaction mixture of **5** and nitroarene **14b** at room temperature for 4 h shows the formation of the nitrone **15b** along with **2b**. The same mixture on stirring for 4 h at 60 °C produces **2b** in 55-60% yield.



17 : R^1 = R^2 = H; **19**
18

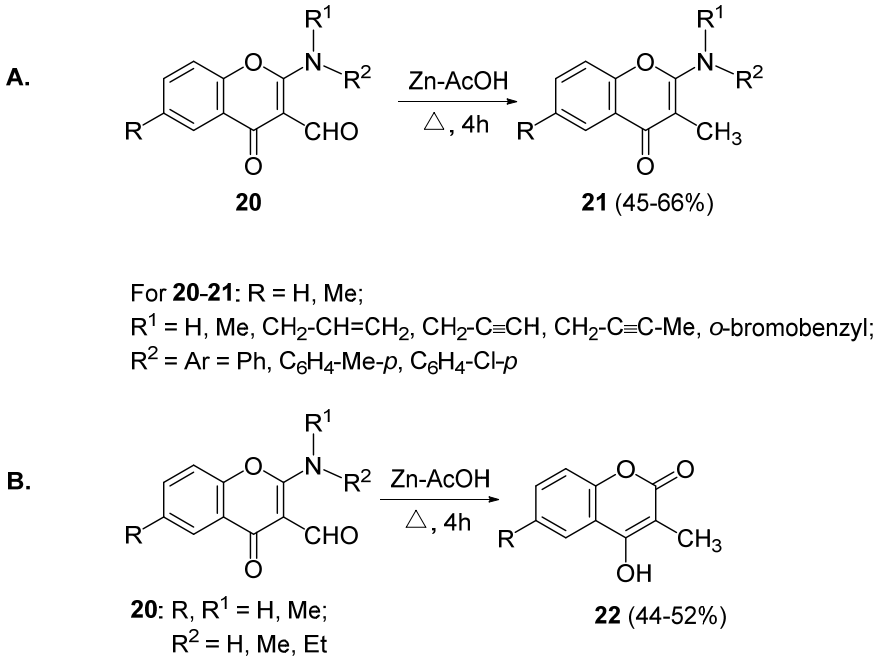
For **18** and **19** : R^1R^2 = CH=CH-CH=CH



Preparation of 2-(*N*-alkyl-*N*-arylamino)-3-formylchromone **3a** by *N*-alkylation of 2-*N*-arylaminochromone **2b** with alkyl halide is discussed later while describing its reactions. 2-(Dialkylamino)chromones **17** (R = Me, Et) have been formylated at their 3-position with DMF-$POCl_3$ or Cl_2CHOMe in the presence of $TiCl_4$ to afford **4** ($R^1 = R^2$ = Me or Et).[15] DMF-$POCl_3$ formylates the naphthopyranone **18** to 3-formylpyranone **19**.[16]

3. Reduction

The chromone **20** when refluxed with Zn in AcOH gives depending on the nature of the NR^1R^2 group either 2-arylamino-3-methylchromone **21** or 3-methyl-4-hydroxycoumarin **22** as shown in Scheme 3.[17]



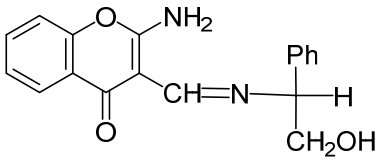
Scheme 3

4. Reactions with Nitrogenous Nucleophiles

4.1. Reaction with amines

4.1.1. Reaction with aliphatic amines. 2-Aminochromone-3-carbaldehyde **1** behaves as a heteroaromatic aldehyde towards an aliphatic primary amine, the resultant Schiff base functioning as a *N*,*N*-donor heterocyclic chelator for several metal ions. As for example, Schiff base ligand **23** (≡ L) derived from the condensation of aldehyde **1** with (*R*)-2-amino-2-phenyl-

ethanol forms a pentacoordinated Cu(II) complex **24** with $Cu(NO_3)_2$ and a tetracoordinated Zn(II) complex **25** with $Zn(NO_3)_2$.[18]



23

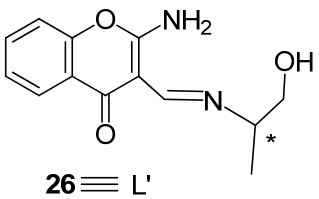
$[CuL_2(H_2O)](NO_3)_2$

24

$[ZnL_2](NO_3)_2$

25

Chiral Schiff bases **26** (≡ L') derived from aldehyde **1** and each enantiomer of 2-aminopropan-1-ol function as tridentate ligands coordinating through their amino nitrogen, imino nitrogen and hydroxy oxygen. These ligands form with copper(II) nitrate and zinc(II) nitrate the pentacoordinated Cu(II) and tetracoordinated Zn(II) complexes **27** and **28** respectively. The DNA binding studies of these complexes with calf thymus reveal that both *R*-**27** and *S*-**27** prefer guanine-cytosine rich region whereas *R*-**28** and *S*-**28** prefer adenine-thymine residues in the major groove of DNA, *R*-**27** showing better DNA cleavage activity.[19] In its reaction with *trans*-$RuCl_2(PPh_3)_2$ in refluxing toluene under an open atmosphere to form the ruthenium complex **30**, the Schiff base **29** behaves differently from the previous two imines **23** and **26**; here the NH_2 group at the pyran 2-position functions as a vinylogous amide and consequently this amino nitrogen is covalently (not coordinately as in **23** and **26**) bonded to the tripositive ruthenium arising from air oxidation of Ru(II).[20]



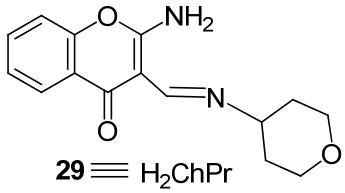
26 ≡ L'

$[CuL'(H_2O)(NO_3)]NO_3$

27

$[ZnL'(NO_3)]NO_3$

28

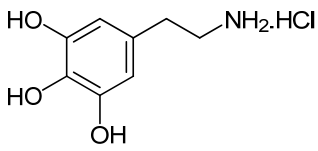


29 ≡ H_2ChPr

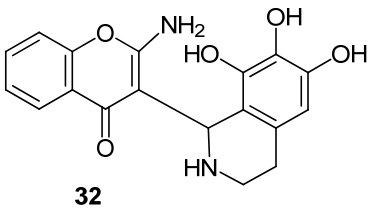
$[Ru^{III}Cl(HChPr)(PPh_3)]_2(u\text{-}Cl)_2$

30

Pictet-Spengler reaction of 5-hydroxydopamine hydrochloride **31** with the aldehyde **1** gives 1-(1-benzopyran-3-yl)isoquinoline derivative **32**.[21]



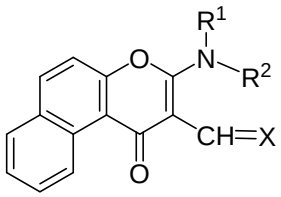
31



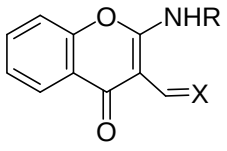
32

2-(*N*,*N*-Disubstituted amino)chromone-3-aldehydes **3** and **4** behave differently from their *N*-unsubstituted analogue **1** towards an aliphatic primary amine or diamine. A primary amine

instead of initially condensing with the aldehyde function of **3** and **4** undergoes an aza-Michael addition to their α,β-unsaturated carbonyl moiety with concomitant expulsion of the nucleofugal disubstituted amine; the net result is thus an amine exchange reaction.[22-28] As for example, in 8-isopropyl-5-methyl-2-(dimethylamino)chromone-3-aldehyde on treatment with tri- or penta-methylenediamine the dimethylamino group is replaced by $NH(CH_2)_nNH_2$ (n = 3 or 5).[22,23] Reactions involving equimolar amounts of **19** and *n*-propanamine in refluxing toluene gives the amino-aldehyde **33** that can react with a second molecule of *n*-propanamine giving the imine **34**.[24] Similarly in refluxing MeCN-H_2O (65:25) the aminochromone **3** gives **35** with one equivalent of a primary aliphatic or aromatic amine RNH_2 but **36** with two equivalents of the same amine.[25] A similar amine exchange reaction in the aminochromone **3b** is presented in Section 9.



	X	R^1	R^2
19	O	Me	Me
33	O	H	*n*-Pr
34	N-Pr-*n*	H	*n*-Pr

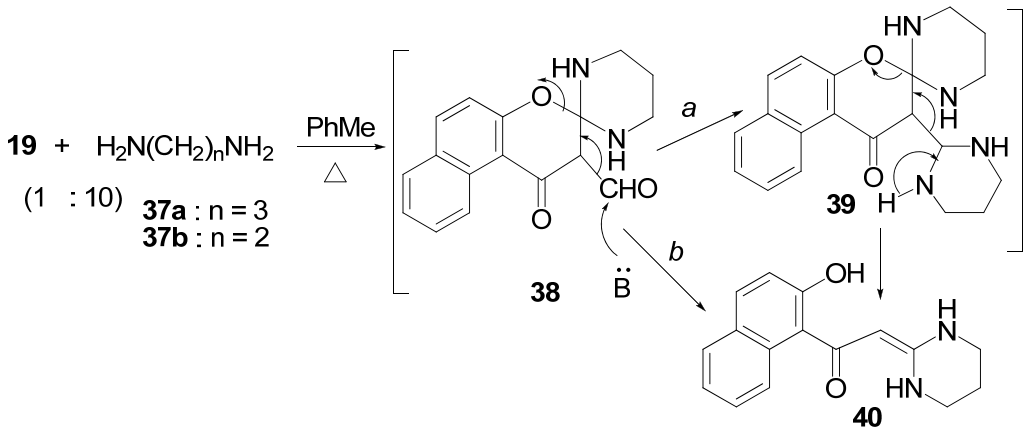


35 : X = O
36 : X = NR

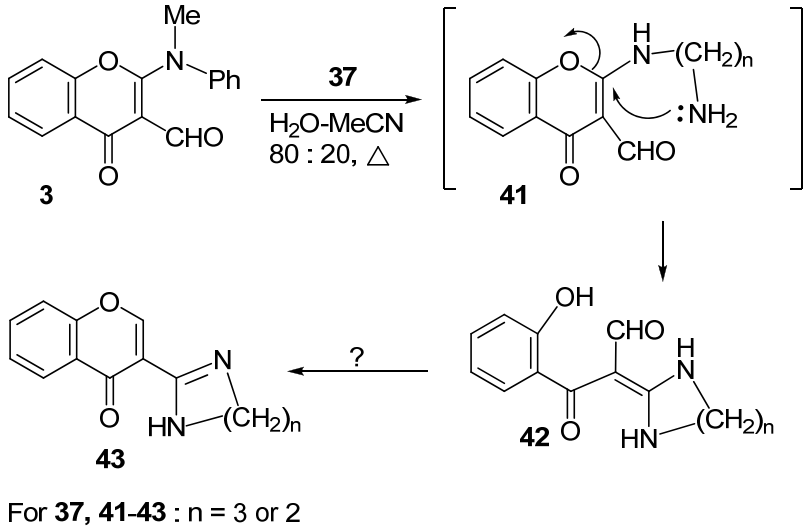
For **35** and **36** :
R = benzyl, *n*-butyl, *o*-anisyl, *p*-tolyl, *p*-chlorophenyl, 2-naphthyl

Sottofattori *et al.*[24] have obtained 2-methylenetetrahydropyrimidine **40** by reacting the aldehyde **19** with an excess of propane-1,3-diamine **37a** in refluxing toluene and suggested a mechanism for the reaction as depicted in Scheme 4, path *a*. The intermediate **38** arising from **19** and **37a** through an amine exchange and subsequent intramolecular Michael addition condenses with a second molecule of **37a** (path *a*); the resultant intermediate **39** undergoes fragmentation to **40** and 3,4,5,6-tetrahydropyrimidine. The present authors opine that nitrogen bonded hydrogen of the hexahydropyrimidine moiety in **39** is not at all acidic and so it is quite unlikely to trigger under base catalysis the suggested fragmentation (path *a*). Contrarily, the secondary amino group of the intermediate **38** is evidently more nucleophilic than the primary amino group in **37a**; hence the base-catalyzed deformylative pyran ring opening of **38** to **40** is more facile, the intermediate **38** itself functioning as the catalyst (path *b*).

The reaction course for the reported formation of the nitrogen heterocycles **42** via **41** from the aldehyde **3** and diamine **37** in hot aqueous acetonitrile (80:20) (Scheme 5)[26] differs from that for the formation of **40** from the allied aldehyde **19** and **37a** (Scheme 4), the reaction conditions most probably influencing the reaction outcome. The possible conversion of **42** into **43** was not attempted.

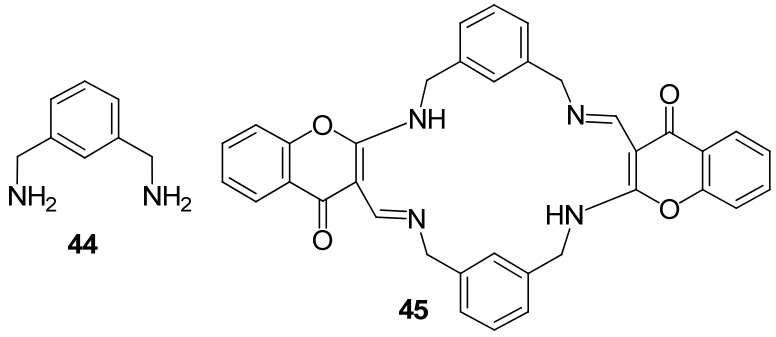


Scheme 4

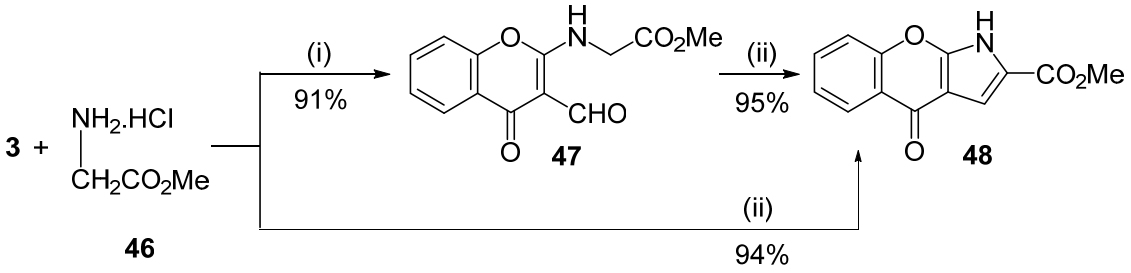


Scheme 5

When an equivalent amount of the aldehyde **3** and *m*-xylylenediamine **44** are refluxed together in MeCN, a [2+2] macrocycle **45** is formed in 96% yield.[27]

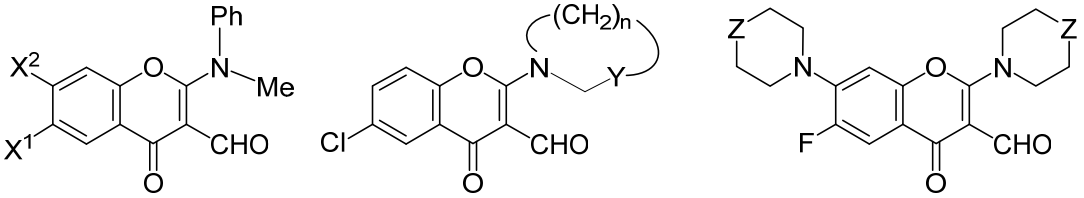


An interesting reaction of the aldehyde **3** with methyl glycinate hydrochloride **46**, ultimately yielding through **47** the pyrrolo[2,3-*b*][1]benzopyran **48**, is depicted in Scheme 6.[27]

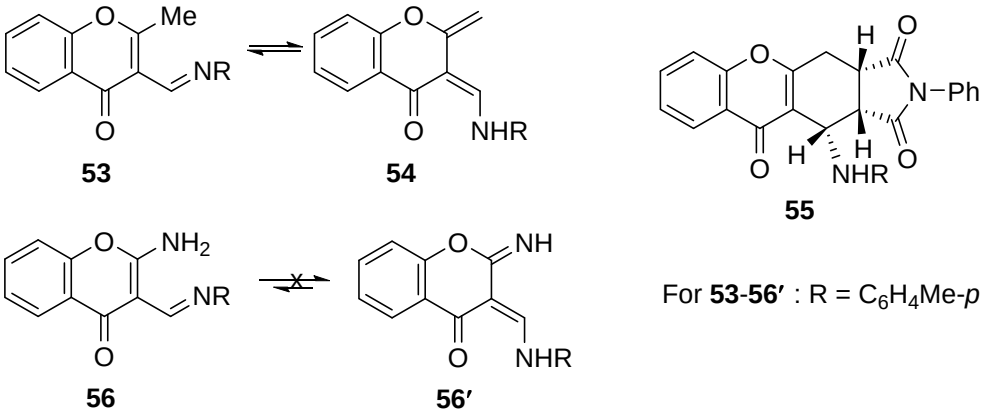


Scheme 6. Reagents and conditions: (i) H_2O:MeCN (80:20), Et_3N, Δ; (ii) H_2O:MeCN (80:20), K_2CO_3, Δ.

Many cyclic amines like pyrrolidine, piperidine, morpholine *etc*. can bring about amine exchange reactions in aminochromone **3**.[25] The 2-aminochromones **49** and **50** on treatment with the appropriate cyclic amine in refluxing MeCN furnish the respective amine exchange products **51** and **52** which are potential topoisomerase inhibitor anticancer agents.[28]

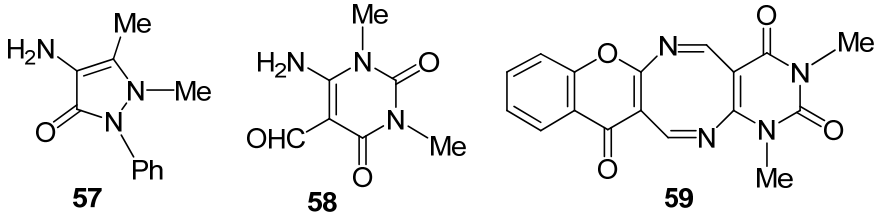


4.1.2. Reaction with aromatic amines. 2-Methyl-3-iminomethylchromone **53**, a Schiff base of the aldehyde **8**, gives through its dienamine tautomer **54** with *N*-phenylmaleimide (NPMI) the [4+2]cycloadduct **55**. In contrast, 2-amino-3-iminomethylchromone **56** does not tautomerize to **56′**, the aza-analogue of the diene **54**, and hence it fails to undergo a hetero-Diels-Alder reaction with any dienophile. The imine **56** when heated with either dimethyl acetylenedicarboxylate (DMAD) or NPMI in DMF under reflux simply undergoes self-condensation to the diazocine **9**.[29]



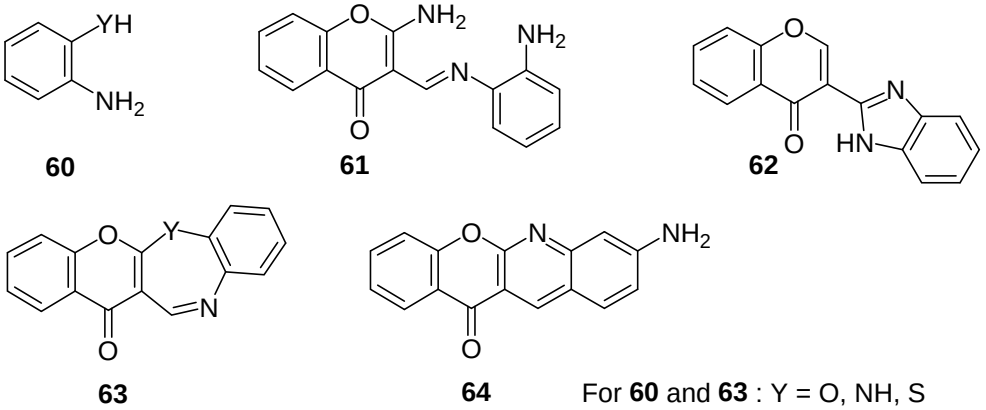
53 **54** **55** **56** **56′**

The condensation of the aldehyde **1** with 2-aminoacetophenone and 4-aminoantipyrine **57** in boiling ethanol containing a catalytic amount of H_2SO_4 gives the corresponding Schiff bases whereas that with 6-amino-1,3-dimethyluracil-5-carboxaldehyde **58** gives the doubly fused diazocine **59**.[30]



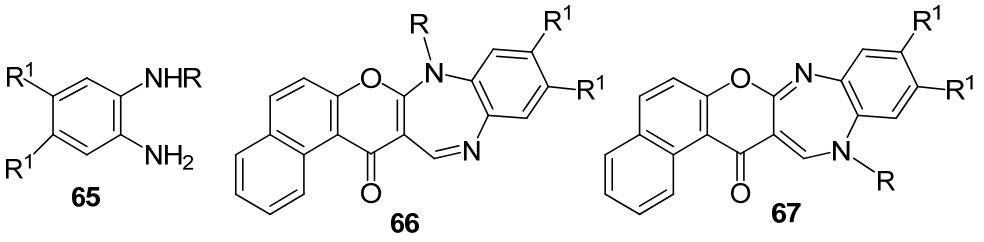
57 **58** **59**

3-Iminomethylchromone **61**, derived from the aldehyde **1** and *o*-phenylenediamine **60** (Y = NH) in refluxing EtOH, transforms on boiling in AcOH to the benzimidazole **62**, the mechanism of this transformation having been duly discussed.[31] The aminoaldehyde **3** and the amine **60** when refluxed together in MeCN-H_2O (80:20) give the tetracycle **63**;[25,27] reaction between **3** and *m*-phenylenediamine under the same conditions gives the pyranoquinoline **64**. A [3+3] macrocycle results from refluxing in xylene a mixture of **3** and *m*-aminophenol.[27]



60 **61** **62** **63** **64**

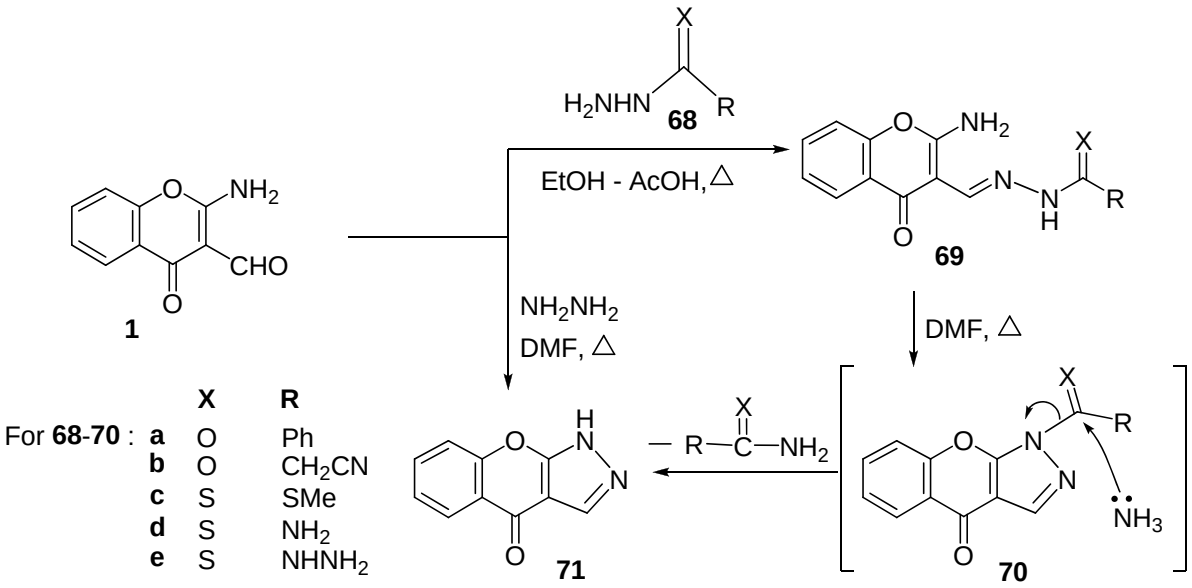
A mixture of the aminoaldehyde **19** (NR_2 = NMe_2) and *o*-phenylenediamine **65** (R = H, Me, Ph, *p*-C_6H_4Cl) when heated in AcOH under reflux produces the fused 1,5-diazepine **66** (66-94%). The reaction of the aforesaid aldehyde with a monosubstituted diamine **65** (R ≠ H) in refluxing pyridine generally affords **66** in low yield (~ 20%), it being associated with its isomer **67** (~ 8%).[32]



For **65**-**67** : R^1 = H, Me

4.2. Reaction with hydrazines

All the chromone-3-aldehydes **1**-**4** irrespective of the nature of the amino group at their pyran 2-position get derivatized through their aldehyde function by the hydrazide NH_2NHY to the corresponding hydrazones that may undergo further transformation depending on the nature of their NR^1R^2 and NHY groupings. The aldehyde **1** with the hydrazine **68** in boiling ethanol containing a catalytic amount of acetic acid gives the hydrazone **69** that in refluxing DMF is converted through **70** into the pyranopyrazole **71**, also available by heating **1** with hydrazine hydrate in DMF under reflux (Scheme 7).[30] The amine **3** with hydrazine in hot aqueous MeCN (80:20) also produces **71**.[25]

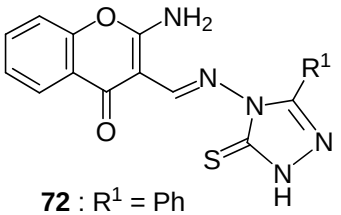


For **68**-**70** :

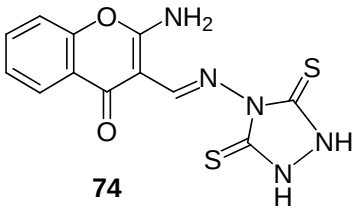
	X	R
a	O	Ph
b	O	CH_2CN
c	S	SMe
d	S	NH_2
e	S	$NHNH_2$

Scheme 7

The thiocarbohydrazone **69e** in pyridine on being heated with PhCOCl, Ac_2O and CS_2 gives the triazoles **72**, **73** and **74**, respectively.[30] Heterocyclization of the –NH-C(=X)$NHNH_2$ functionality of **69e** with some 1,2-bifunctional electrophiles as ClCOCOCl, $ClCH_2COCl$, $PhCOCH_2Br$, $BrCH(CN)_2$ and $MeCOCO_2Na$ leading to the appropriate 1,2,4-triazole derivatives has also been reported.[30]

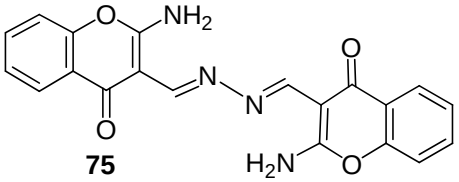


72 : R^1 = Ph
73 : R^1 = Me

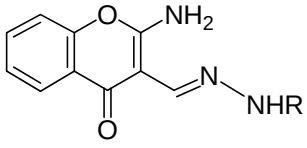


74

A mixture of the aldehyde **1** and hydrazine hydrate on being heated with triethylammonium bisulfate (20 mol%) at 120 °C under solvent free conditions affords the bis-hydrazone **75**.[33] The hydrazone **76** (R = Ph), preferentially prepared in quantitative yield by reacting 3-cyanochromone **7** with phenylhydrazine in boiling benzene or benzene-triethylamine, on being heated in ethanol containing 20% H_2SO_4, is converted into the pyrazole **77**.[34] The hydrazone **76** (R = 2,4-dichlorophenyl, CO_2Me, CH_2CH_2OH) and the bis-hydrazone **78**, derived from **1** and benzophenone hydrazone, have been evaluated for cytotoxicity (MTT test) against H2-60 and NALM-6 leukemia cells.[35] The hydrazone **76** (R = CO_2Et), obtained from **1** and ethyl carbazate, on heating with ethyl chloroformate gives the carbazate **79** instead of any cyclized product.[36] The hydrazone **80** obtained by heating the amine **1** with 5,6-diphenyl-1,2,4-triazin-3-ylhydrazine in CF_3COOH acts as a fluorophore.[37] Cytotoxicity of the hydrazone **81** derived from **1** and *N*-amino-*N'*-hydroxyguanidine against several tumor cells has been studied.[38]



75



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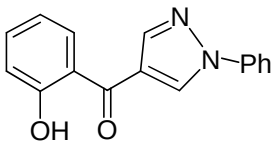

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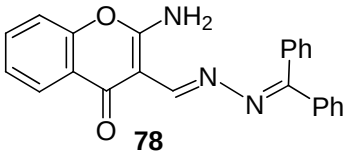

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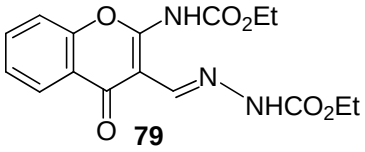

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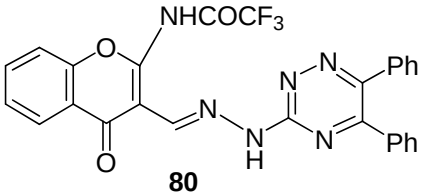
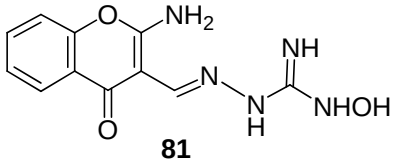


80

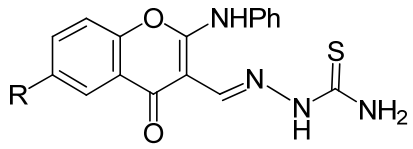


81

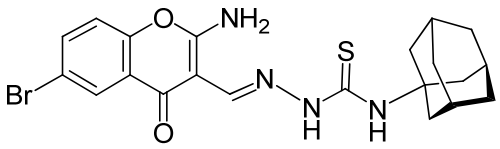
The thiosemicarbazone **69d** functions as a tridentate ligand. It is represented as ligand L when an electron lone pair on sulfur of its –NH-C(=S)NH_2 grouping is coordinated to the metal but as L' when the sulphide derived from its –N=C(NH_2)SH grouping is covalently bonded to the metal. The compound **69d** gives with copper(II) acetate, sulfate, nitrate, chloride, bromide and perchlorate the Cu(II) complexes **82** – **87**, respectively. Cu(II) complexes with this thiosemicarbazone ligand and another secondary bidentate ligand as 8-hydroxyquinoline and 1,10-phenanthroline are also reported.[39]

$CuL'(H_2O)(MeCOO)$	$[CuL(H_2O)(SO_4)]$	$[CuL'(NO_3)]$
82	**83**	**84**
$[CuL'Cl].0.5H_2O$	$[CuL'(H_2O)]Br$	$[CuL(H_2O)_3](ClO_4)_2.3H_2O$
85	**86**	**87**

Antibacterial activity of the thiosemicarbazone **88** prepared by treating the appropriate chromone-3-aldehyde with thiosemicarbazide in MeOH containing $Zn(ClO_4)_2$ as catalyst at room temperature against *E.coli* has been assessed.[40] Anticancer activity of the thiosemicarbazone **89** having the chromone and adamantyl moieties against several cell lines has been evaluated.[41]

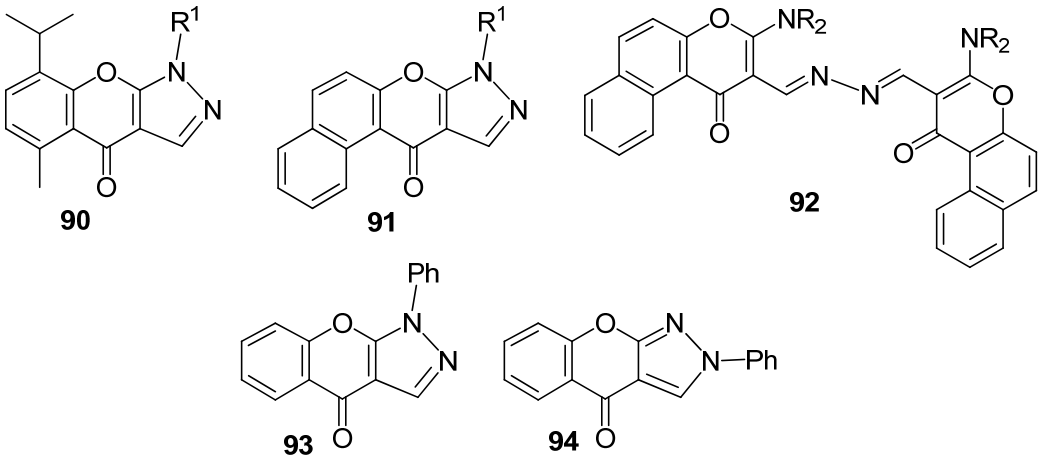


88 : R = H, Me, F, Cl, Br

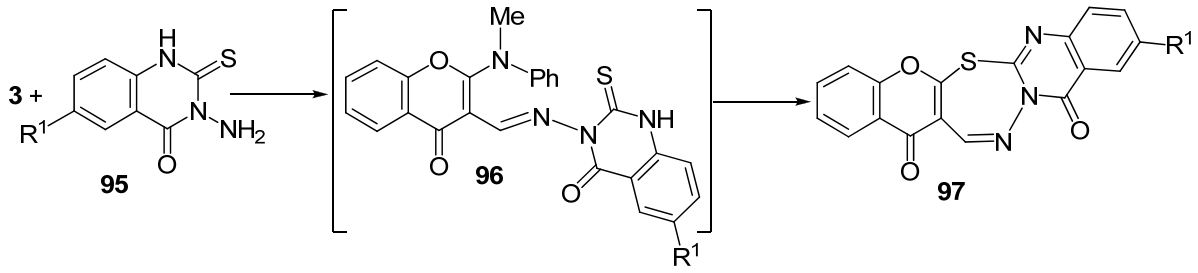


89

Heating an ethanolic solution of 2-(*N*,*N*-dimethyl- or -diethyl-amino)-8-isopropyl-5-methylchromone-3-carbaldehyde together with NH_2NHR^1 (R^1 = H, Me, Ph) affords 1-benzopyrano[2,3-*c*]pyrazole **90**.[15] The amino-aldehyde **19** on warming with NH_2NHR^1 (R^1 = H, Ph) in ethanol for a short time gives the corresponding hydrazone which on prolonged heating in ethanol furnishes naphthopyranopyrazole **91**. In the case of reaction of **19** [R = *i*-C_3H_7; RR = $CH_2(CH_2)_2CH_2$] with hydrazine hydrate, the pyrazole **91** (R^1 = H) remains contaminated with the bishydrazone **92**.[16] When the aldehyde **3** is treated with NH_2NHPh in refluxing MeCN, the product **93** is sometimes accompanied by the isomeric compound **94**.[27]



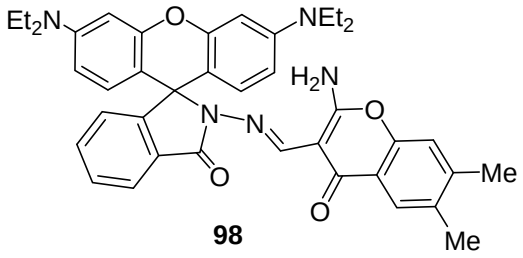
A compound having an amino group bonded to a heterocyclic nitrogen behaves as a *N*,*N*-disubstituted hydrazine rather than a primary amine so as to undergo 1,2- (not 1,4) – addition to the α,β-unsaturated aldehyde functionality of 2-amino-3-formylchromones **1**-**4**. Thus, the 3-aminoquinazoline **95** (R^1 = H, Br) with the chromone **3** gives the hydrazone **96** that spontaneously cyclizes to the pentacyclic system **97** (Scheme 8).[42,43]



Scheme 8

The hydrazone **98** derived from 2-amino-6,7-dimethylchromone-3-aldehyde and rhodamine B-hydrazide shows extremely high fluorescence enhancement upon forming a 1:1 complex with Sn^{4+}; Density Functional Theory (DFT) computational study indicates it to be a nearly planar pentacoordinated Sn(IV) complex, the metal being coordinated with two carbonyl oxygens, the

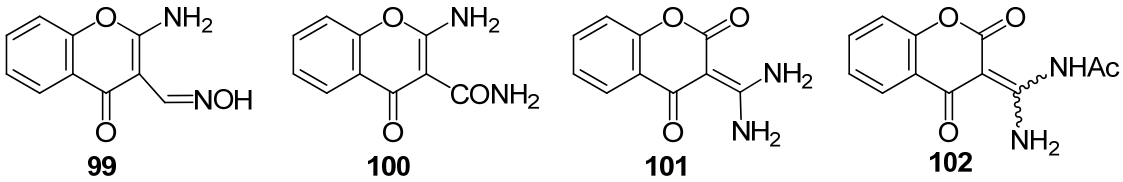
doubly bonded nitrogen and two chloride anions. This complex is selectively and fully reversible in the presence of sulfide anions.[44]



98

4.3. Reaction with hydroxylamine

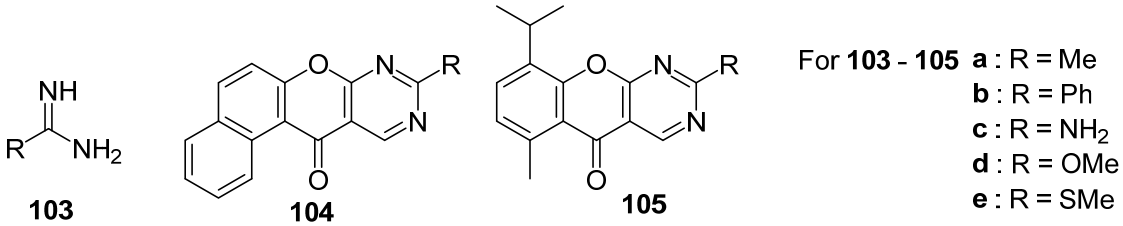
When an ethanolic solution of the aldehyde **1** is heated with $NH_2OH.HCl$ in the presence of an alkali, the initially formed amino-aldoxime **99** (≡ **6**) under alkaline conditions leads to 2-amino-3-carbamoylchromone **100** that on further treatment with NH_2OH gives the chromandione **101**.[45] The mechanisms of these transformations have been duly elaborated.[46,47] The diamine **101** on acetylation forms an *E*, *Z* mixture of the monoacetamide **102**.



99 **100** **101** **102**

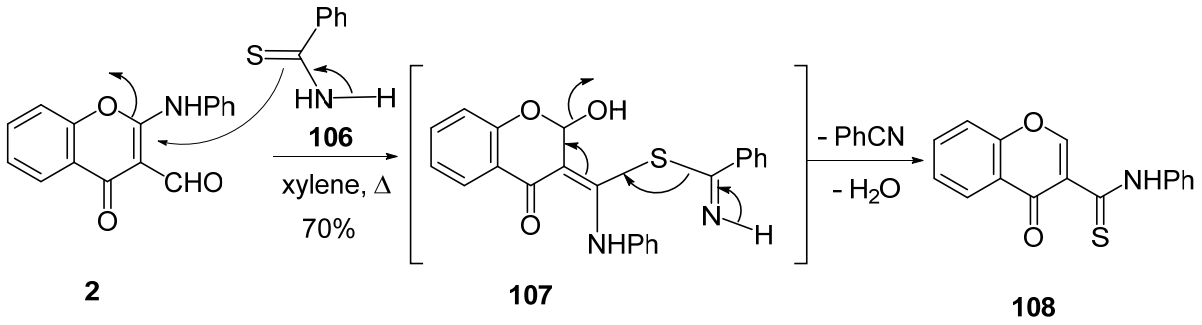
4.4. Reaction with amidines and thioamides

The aldehyde **19** with the amidine **103** gives the benzopyranopyrimidine **104**, acetamidine **103a** and benzamidine **103b** being used as their hydrochloride, guanidine **103c** as its carbonate salt and *O*-methylisourea and *S*-methylisothiourea **103d**,**e** as their sulfates, and pyridine being the reaction medium.[48] The reaction of **19** with **103d** in pyridine gives a product (44%) structurally akin to the fused diazocine **9**; the same reaction in EtOH-NEt_3, however, gives **104d** exclusively.[48] Similarly the pyranopyrimidine **105** (R = Ph, NH_2, SMe) is obtained from the appropriate 2-(*N*, *N*-dialkylamino)chromone-3-aldehyde and the amidine **103**.[15]



103 **104** **105**

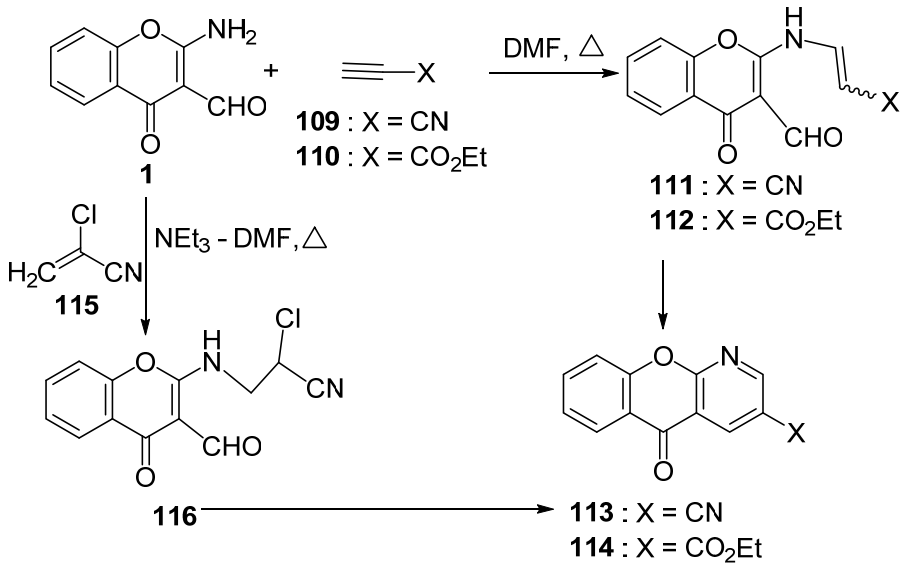
Thia–Michael addition of thiobenzamide (**106**) to the α,β-unsaturated carbonyl functionality of 2-anilino-3-formylchromone (**2**) with concomitant pyran ring opening and recyclization gives the intermediate **107** that eliminates benzonitrile and water giving chromone-3-thioanilide (**108**) (Scheme 9).[49,50]



Scheme 9

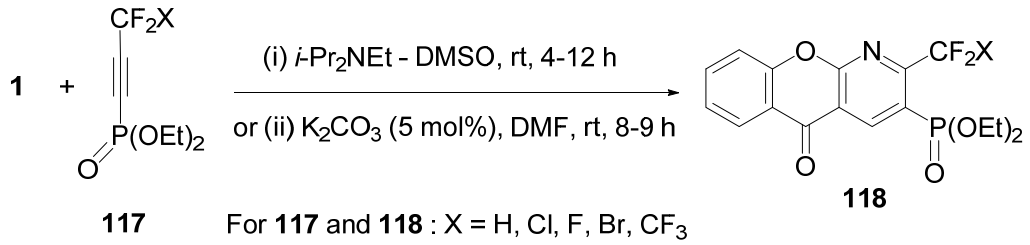
5. Reaction with Activated Alkynes and Alkenes

2-Amino-3-formylchromone **1** in hot DMF undergoes through its amine function an aza-Michael addition to cyanoacetylene **109**, the non-isolable Michael adduct **111** cyclizing to the 5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine **113** (henceforth this fused heterocyclic moiety will be considered as azaxanthone). The aldehyde **1** when heated with ethyl propiolate **110** in Et_3N-DMF gives a mixture of **112** and **114**, the former product on further heating in the above named solvent mixture cyclising to **114**. The aldehyde **1** with α-chloroacrylonitrile **115** gives through the intermediate **116** (isolable) the azaxanthone **113** (Scheme 10).[4,5]



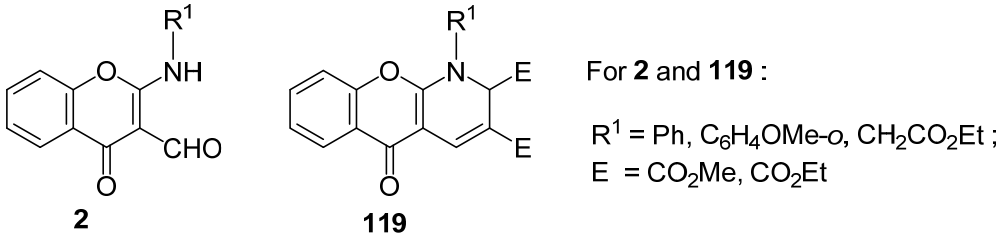
Scheme 10

The acetylenephosphonate **117** carrying a CF_2X group has been employed in a base mediated heterocyclization reaction with the aldehyde **1** to give the 3-difluoromethyl-4-azaxanthon-2-ylphosphonate **118** (Scheme 11).[51] Condensation of **1** with **117** (X = H, Cl, F, CF_3) is best suited by method (i) and that with **117** (X = Br) by method (ii).

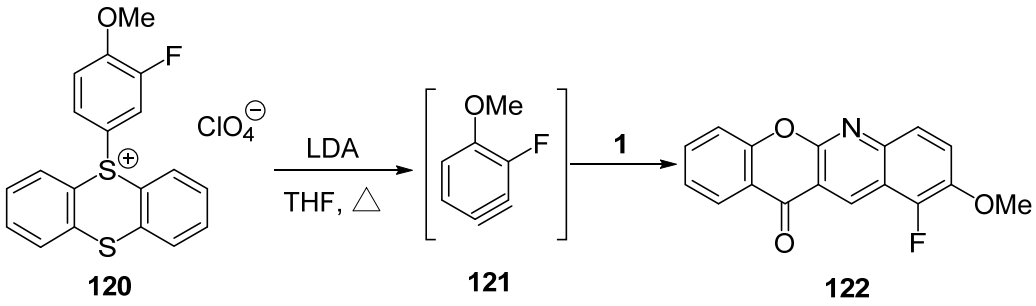


Scheme 11

Trapping by the aminoaldehyde **2** of the highly reactive 1:1 intermediate generated in the reaction between dialkyl acetylenedicarboxylate and triphenylphosphine in dichloromethane at ambient temperature results in the formation of the 3,4-dihydro-4-azaxanthone **119**.[52]



Heterocyclization of the aminoaldehyde **1** with benzyne is also known. 3-Fluoro-4-methoxybenzyne **121** generated from 5-(3-fluoro-4-methoxyphenyl)thianthrenium perchlorate **120** and LDA in THF at reflux reacts with the chromone **1** to give the 1-benzopyrano[2,3-*b*]-quinoline **122** in 70% yield (Scheme 12).[53]

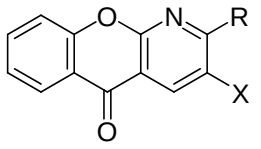


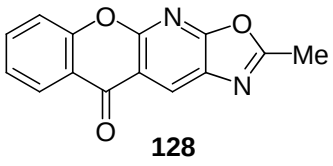
Scheme 12

6. Friedländer Annulation

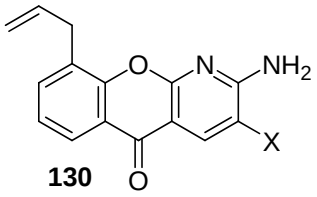
6.1. Annulation with active methylene compounds

Friedländer annulation of the aldehyde **1** with compounds having either a $–CH_2CO-$ or a $-CH_2CN$ grouping has received a fillip since an earlier report on the synthesis of 4-azaxanthone derivatives **123**-**125** by a base catalyzed reaction of **1** with diethyl malonate, ethyl cyanoacetate and malononitrile, respectively.[3] The aldehyde **1** with acetylacetone and ethyl acetoacetate in hot EtOH-piperidine gives **126** and **127** respectively.[54] All these azaxanthones **123**-**127** have also been obtained in higher yields by reacting the nitrile **7**, the chemical equivalent of **1**, with the appropriate active methylene compounds under base catalysis.[54,55] A mixture of **1** and acetylglycine heated in Ac_2O containing fused NaOAc under reflux produces the benzopyrano[2,3-*b*]pyridino[3,2-*d*]-oxazolone **128**.[6] 2-Amino-3-formyl-benzo[*f*]- and -benzo[*h*]-chromone behave similarly as their unsubstituted 2-amino-3-formylchromone **1** towards the above mentioned active methylene compounds.[56] Friedländer annulations of 8-allyl-2-amino-3-formylchromone with the cyano compound **129** (X = CN, SPh, $CONH_2$, CO_2Et) in refluxing EtOH-DBU gives the azaxanthone **130**.[57] 2-Amino-3-formyl-6-methylchromone with **129** (X = -CONHN=CHAr) under similar condition gives the product **131**.[58]





128

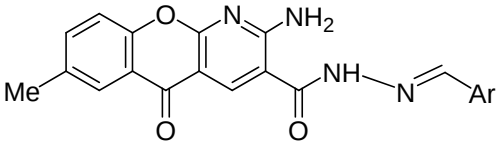


130

	R	X
123	OH	CO_2Et
124	NH_2	CO_2Et
125	NH_2	CN
126	Me	COMe
127	Me	CO_2Et

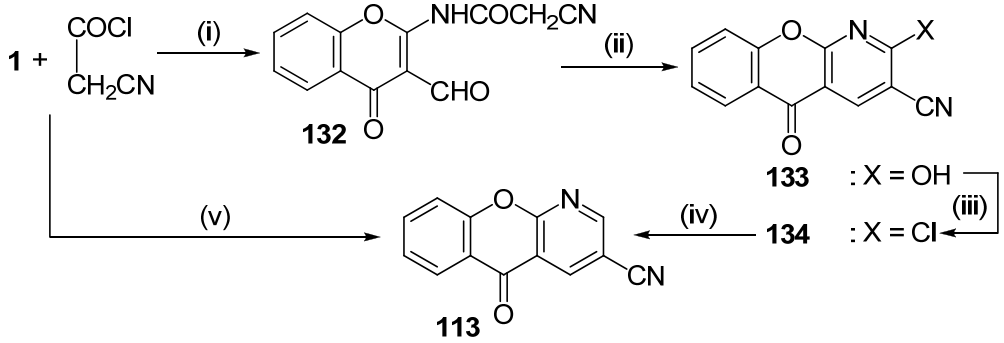
$NCCH_2X$

129

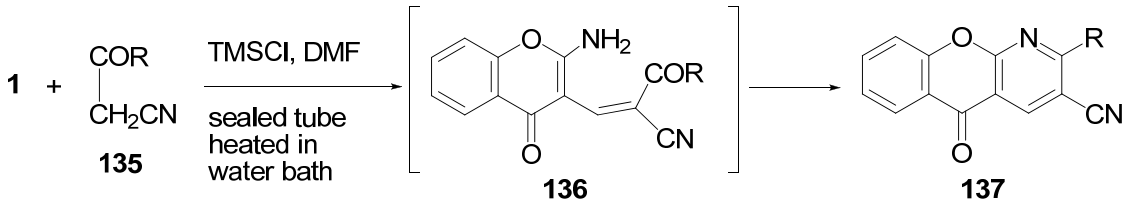


131 : Ar = C_6H_4Cl-*p*

The aldehyde **1** is acylated by cyanoacetyl chloride in CH_2Cl_2 to **132**; its cyclization product **133** is converted through **134** to 2-cyano-4-azaxanthone **113** obtainable also by heating a mixture of **1** and cyanoacetyl chloride with Vilsmeier reagent (Scheme 13).[4,5]



Scheme 13. Reagents and conditions : (i) CH_2Cl_2, warm; (ii) pyridine, Δ; (iii) $POCl_3$-PCl_5, 120 °C; (iv) Pd-C, H_2, DMF-K_2CO_3, rt; (v) $POCl_3$-DMF.

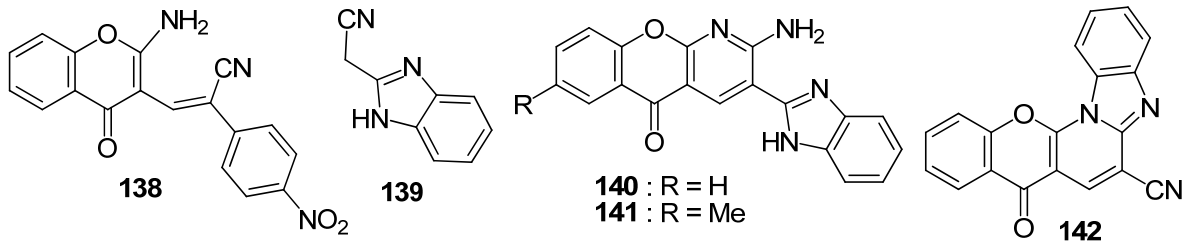


For **135-137** : R = *p*-chlorophenyl, thiophen-2-yl, benzofuran-2-yl

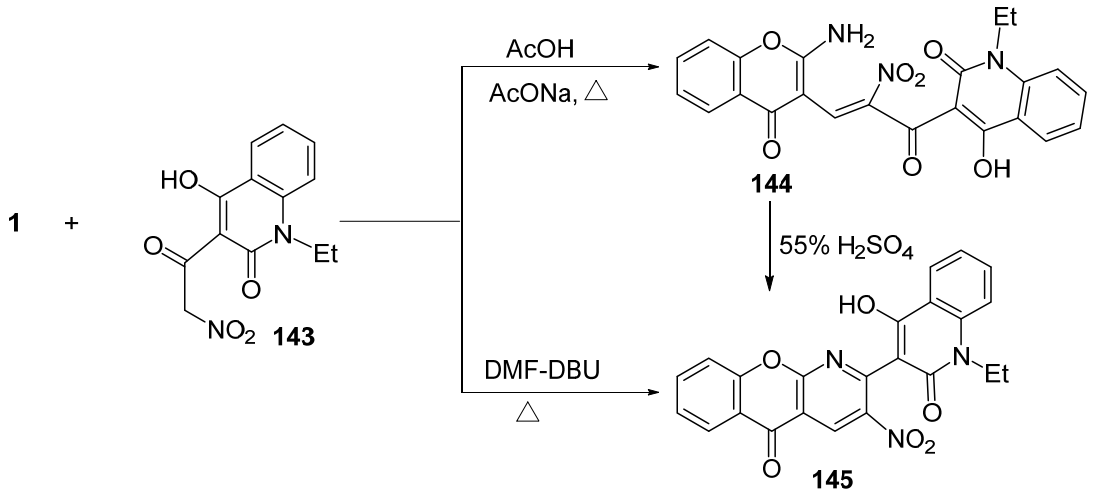
Scheme 14

Ryabukhin *et al.*[59] condensed the aldehyde **1** with acylacetonitrile **135** and obtained through **136** the 2-cyanoazaxanthone **137** (Scheme 14) with complete exclusion of any 2-acyl-3-aminoazaxanthone derivative.

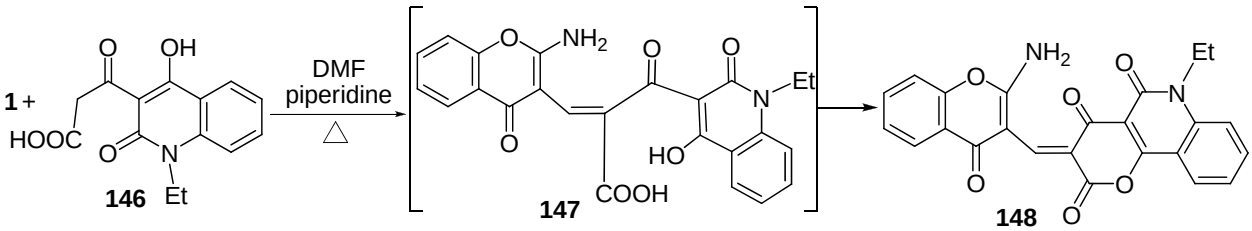
Aryl- and hetaryl- acetonitriles have also been condensed with the aldehyde **1**. The heterogeneous catalyst silica chloride (SiO_2-Cl) prepared by treating oven dried silica gel in dry CH_2Cl_2 with $SOCl_2$ at room temperature, induces Knoevenagel condensation of **1** with *p*-nitrophenylacetonitrile in ethanol at room temperature to give selectively the *Z*-isomer **138** in ~90% yield.[60] No attempt has been made to cyclize **138** to 3-amino-2-(*p*-nitrophenyl)-4-azaxanthone. Condensation of **1** with benzimidazol-2-ylacetonitrile **139** in boiling EtOH-NEt_3 affords the azaxanthone **140** in 65% yield.[61] Under similar conditions the nitrile **139** with 3-cyanochromone **7** and its 6-methyl homologue produce the chromeno[3,2-*e*]pyrido[1,2-*a*]benzimidazole **142** and **141**, respectively.[61]



The results obtained by condensation of the chromone **1** with the acylnitromethane **143**[62] and β-ketoacid **146**[63] are depicted in Schemes 15 and 16, respectively. The stereochemistry of the condensate **144** is not ascertained; it is, however, convertible into the azaxanthone **145**. No intermediate is isolable in the formation of **145** by reacting **1** with **143** in refluxing DMF-DBU. The condensate **147** is most probably formed in *E*-isomeric form so as to undergo lactonization to **148** instead of giving any lactam.

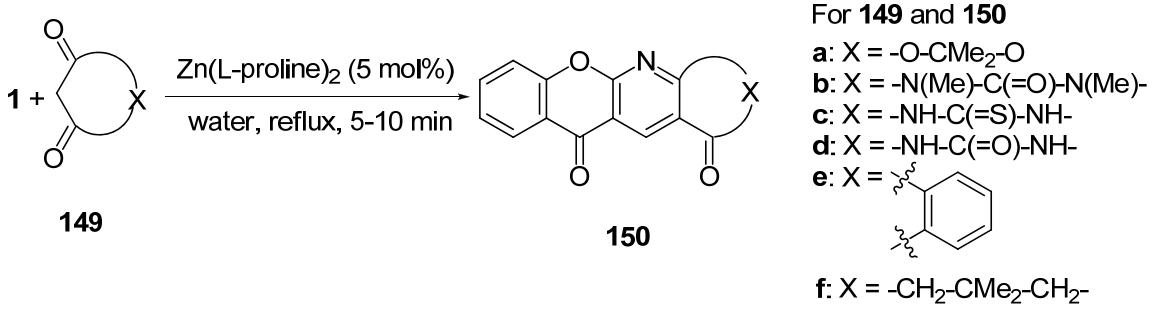


Scheme 15



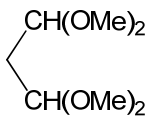
Scheme 16

Siddiqui[64] has developed a facile and green synthetic route to new benzopyrano[2,3-*b*]pyridines **150a-e** in excellent yields (~90%) via Friedländer condensation of the chromone **1** with cyclic active methylene compounds **149** containing a –CO-CH_2-CO- grouping in the presence of Zn(L-proline)$_2$ as an efficient and stable Lewis acid catalyst in water (Scheme 17). Compounds **150d**[57] and **150f**[56] have also been synthesized by base catalyzed reaction of **1** with **149d** and **149f**, respectively.

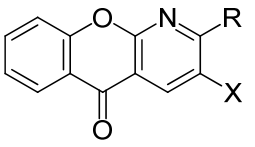


Scheme 17

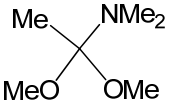
Compounds having their CH_2CO grouping protected as dialkyl acetal can also condense with the aminochromone **1**. Thus, malondialdehyde tetramethyl acetal **151** reacts with **1** in ether containing $BF_3 \cdot Et_2O$, HCO_2H at 60°C to give the 2-formylazaxanthone **152** together with a small amount of its deformylated product **153**.[4,5] *N*,*N*-dimethylacetamide dimethyl acetal **155** and 1-methylpyrrolidine-2-one diethyl acetal **156** give with **1** the condensed products **154** and **157**, respectively.[65]



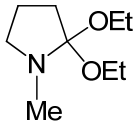
151



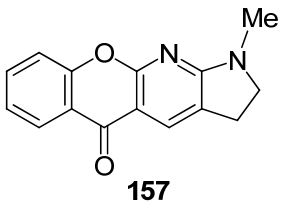
152 : R = H, X = CHO
153 : R = X = H
154 : R = NMe_2, X = H



155

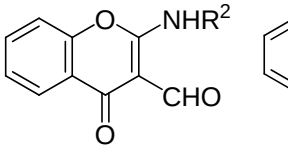


156

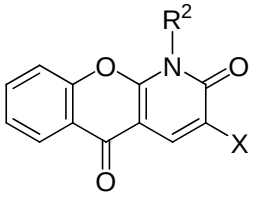


157

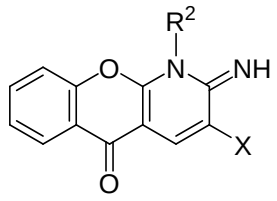
Maiti *et al.*[66] have extensively studied the condensation of 2-(monosubstituted amino)-3-formylchromone **2** with several active methylene compounds. Condensation of **2** with Meldrum's acid, ethyl acetoacetate, ethyl benzoylacetate, diethyl malonate and hippuric acid gives pyranopyridones **158a-e,** respectively. Acetonitrile XCH_2CN (X = CO_2Et, CN), however, reacts differently with **1** under the same conditions to produce via the rarely isolable intermediate **159** the salicyloylpyridone **160**. The aminochromone **161** (R^2 = Me, Et) behaves similarly to **2** in its reaction with ethyl benzoylacetate, diethyl malonate and ethyl nitroacetate in refluxing pyridine-piperidine, but the fused pyridine **162** (X = CN, PhCO) analogous to **159** is formed by reacting **161** (R^2 = Et) with XCH_2CN (X = CN, PhCO).[67] The compound **158** (R^2 = Ph, $PhCH_2$; X = H) is obtained by heating a mixture of the appropriate aminochromone **2** and $Ph_3P{=}CHCO_2Et$ in benzene under reflux.[68]



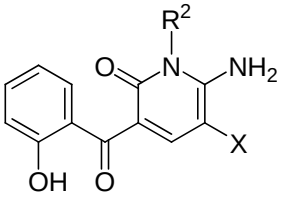
2: R^2 = Et, Ph, C_6H_4Me-*p*



158
a : X = CO_2H
b : X = COMe
c : X = COPh
d : X = CO_2Et
e : X = NHCOPh



159



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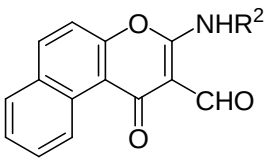
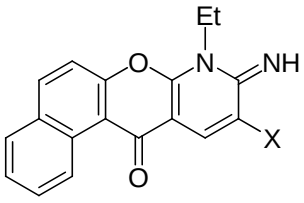


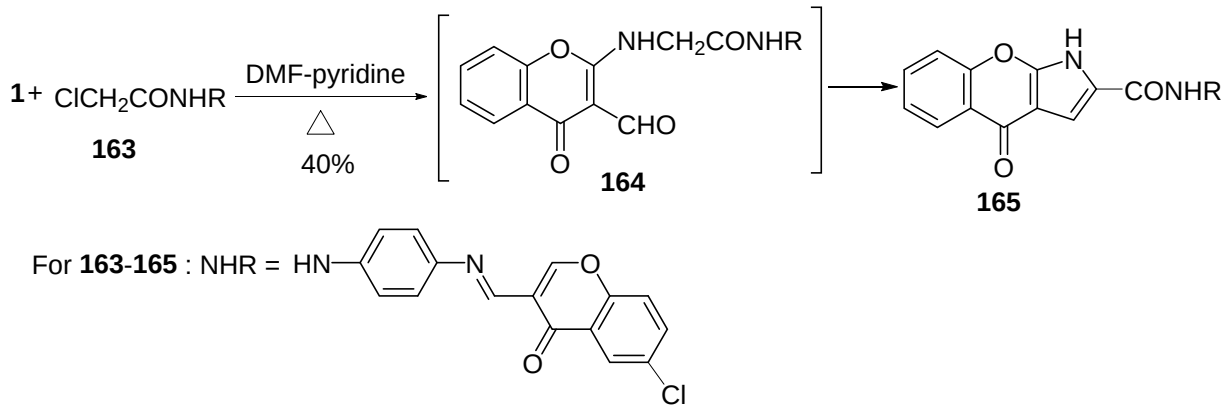
161



162

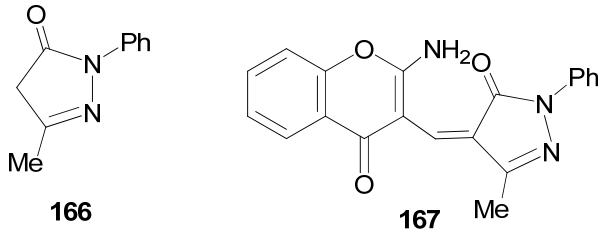
Some reactive methylene compounds take a reaction course other than Friedländer annulation with the amino-aldehyde **1**. As for example, chloroacetamide **163** reacts with the

aldehyde **1** to give the pyrrolopyran **165** via **164** (Scheme 18).[69] The compound **165** shows high activity against *Alternaria alternata*, *Aspergillus niger* and *A. flavipes*.



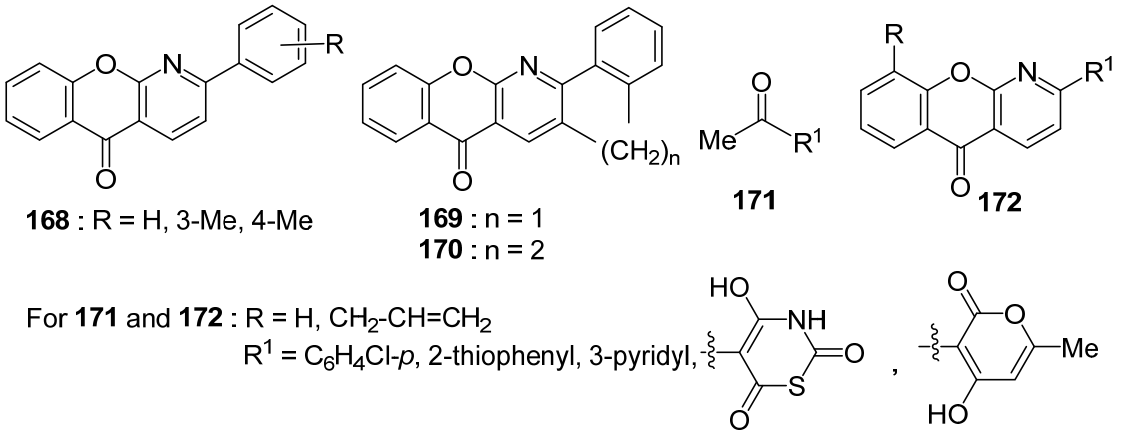
Scheme 18

When an intimate mixture of the aldehyde **1**, phenylhydrazine, ethyl acetoacetate, SiO_2, catalytic amount of $ZnBr_2$ and a small amount of water is subjected to microwave heating at 60°C for 10-15 min, the compound **167** (95%) results.[70] In this one-pot three-component reaction the phenylhydrazine at first forms with ethyl acetoacetate the pyrazolidinone **166** that condenses with **1** giving **167**.



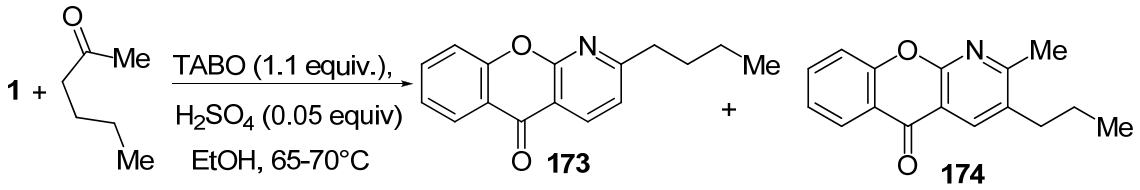
6.2. Annulation with aryl and hetaryl methyl ketones

The azaxanthones **168-170** are obtained by treating the chromone **1** with acetophenone, 1-indanone and 1-tetralone, respectively under mild reaction conditions (4:1 MeCN-H_2O, rt, 8 h) by employing $AuCl_3$-$AgSbF_6$ catalyzed aldol reaction as the key step.[71] The chromone **1** as well as its 8-allyl analogue on condensation with the ketone **171** in refluxing EtOH-DBU gives the azaxanthone **172**.[72,73]



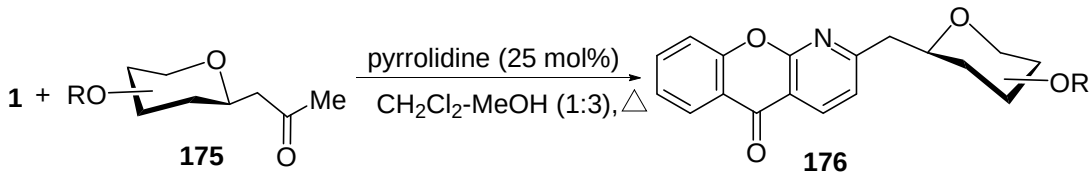
6.3. Annulation with alkyl methyl ketones

Highly regioselective Friedländer annulation of hexan-2-one with the chromone **1** employing 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (TABO) as a catalyst gives the products **173** and **174** in 4:1 proportions (Scheme 19), the major product **173** being obtained in nearly 70% yield.[74]



Scheme 19

Regioselective facile Friedländer synthesis of four different sugar based azaxanthone derivatives of the general structure **176** (Scheme 20) has been achieved and their activity against different microbes assessed.[75]

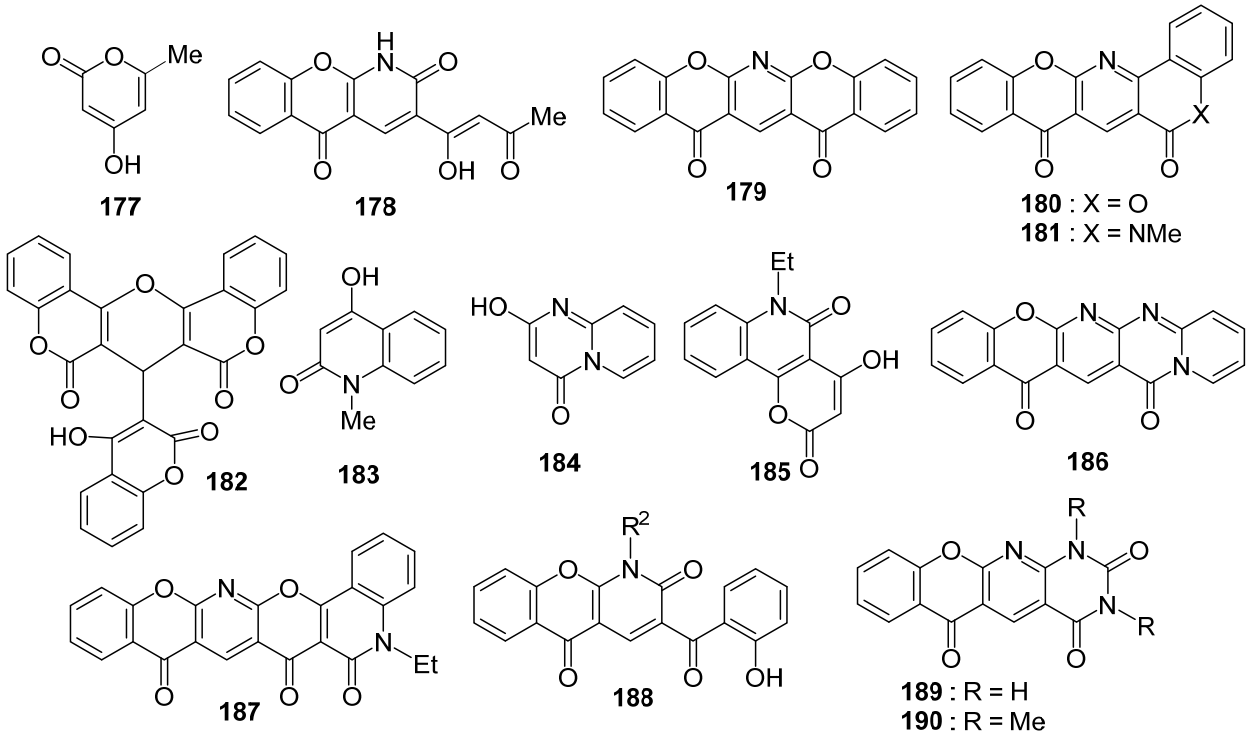


For **175** and **176** : OR represents a number of OH or OAc groups in the pyanose sugars

Scheme 20

6.4. Annulation with enols and enamines

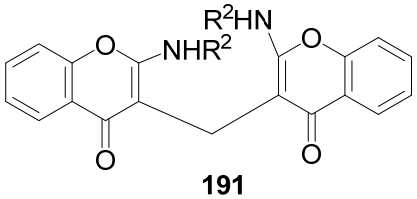
Triacetic acid lactone (TAL) **177** has been annulated with the chromone **1** in pyridine-piperidine at room temperature to yield the pyranopyridine **178**.[76,77] Condensation of 4-hydroxycoumarin



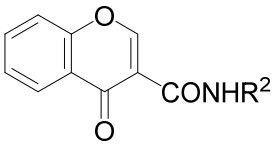
with **1** is reported to give one or more of the products **179**, **180** and **182**.[77-81] Heating the chromone **1** in isopropanol-HCl[78] or a mixture of **1** and 4-hydroxycoumarin in MeOH-pyridine[77] gives the pentacycles **179** and **180** associated with the tricoumarol **182**,[79] but only **180** in refluxing ethanol[80] or DMF-DBU.[81] The heterocyclic enols **183**-**185** with the chromone **1** in refluxing DMF-DBU afford the fused azaxanthones **181**, **186** and **187**, respectively.[81] 2-(*N*-alkylamino)-3-formylchromone **2** (R^2 = Et, Ph) with 4-hydroxycoumarin in refluxing EtOH-pyridine gives the salicyloylxanthone **188**.[66] The enamines $MeC(NH_2)$=CH-X (X = COMe or CO_2Et) condense with the chromone **1** giving the azaxanthones **126** and **127**, respectively.[56] 4-Aminouracil[81] and 4-amino-1,3-dimethyluracil[56] with the chromone **1** give the tetracycles **189** and **190**, respectively.

7. Amine-Formalin Mediated Conversion of 2-(*N*-Alkyl/aryl-amino)-3-formylchromones

The aminochromone **2** (R^2 = Me, Et, Ph, C_6H_4Me-*p*) when heated with a secondary amine such as sarcosine, piperidine or diethylamine in the presence of excess of formalin in DMF under reflux affords 3,3′-methylenebischromone **191**, the yield of the *N*-aryl- and *N*-alkyl product **191** being ~90% and 43%, respectively.[82] When heated in methanol with glycine in the presence of an excess of formalin, the chromone **2** undergoes organocatalytic rearrangement; 2-arylaminochromone **2** (R^2 = Ph, C_6H_4Me-*p*) gives the anilide **192** but *N*-alkylaminochromone **2** (R^2 = Me, Et) the chroman-2,4-dione **16**.[83]



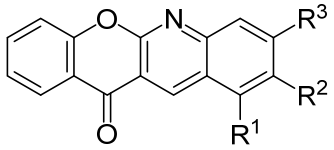
191



192 : R^2 = Ph, C_6H_4Me-*p*

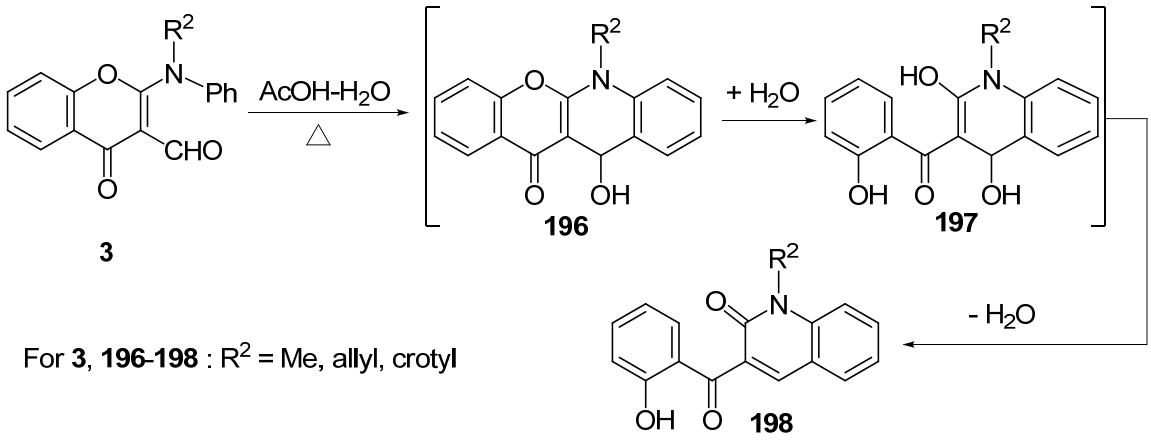
8. Conversion of 2-Arylamino-3-formylchromones into [1]Benzopyrano-[2,3-*b*]quinolones

2-Phenylamino-3-formylchromone **2** cyclizes to the benzopyranoquinoline **193** on refluxing with anhydrous $AlCl_3$ in CCl_4 followed by treatment with sulfuric acid,[11] heating in 70% or conc. sulfuric acid[13,25] or by heating with a secondary amine as sarcosine, piperidine or Et_2NH in DMF under reflux.[82] The chromone **2b** (R^2 = β-naphthyl) on heating in conc. H_2SO_4 transforms into the naphthopyridine **194**.[25] The chromone **3** on treatment with *m*-phenylenediamine in refluxing H_2O-MeCN (80:20) gives the fused quinoline **195** through the intermediacy of the aminochromone **2b** (R^2 = *m*-aminophenyl).[27]



193 : R^1-R^3 = H
194 : R^1R^2 = CH=CH-CH=CH; R^3 = H
195 : R^1 = R^2 = H; R^3 = NH_2

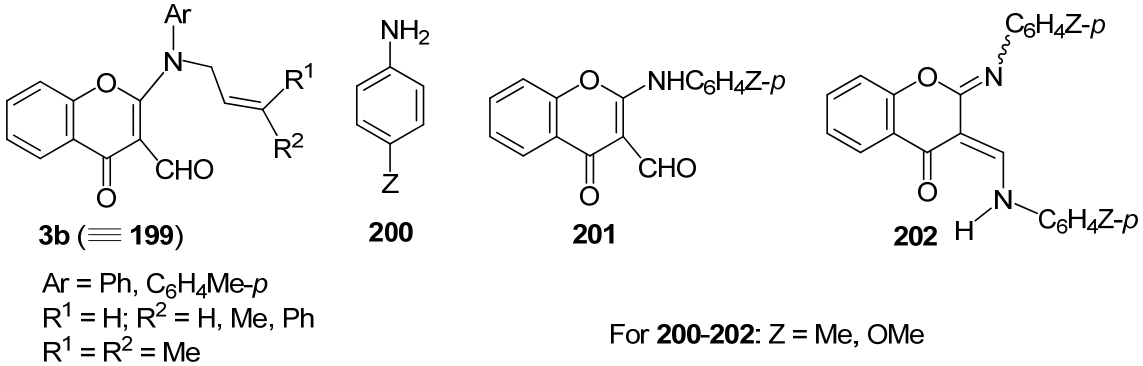
2-(*N*-alkyl-*N*-aryl)chromone **3** obtained by alkylation of the chromone **2** with the appropriate alkyl halide in the presence of K_2CO_3 and NaI in refluxing MeCN is transformed on heating in aq. AcOH into 3-salicyloylquinolin-2-one **198** instead of any fused quinoline derivative (Scheme 21).[84] The *N*-disubstituted aminochromone **3** cyclizes to the fused quinoline **196**; attack of a water molecule at its 5a-position (oxa Michael addition) causes pyran ring opening and the resultant intermediate **197** by tautomerization and water elimination gives **198**.

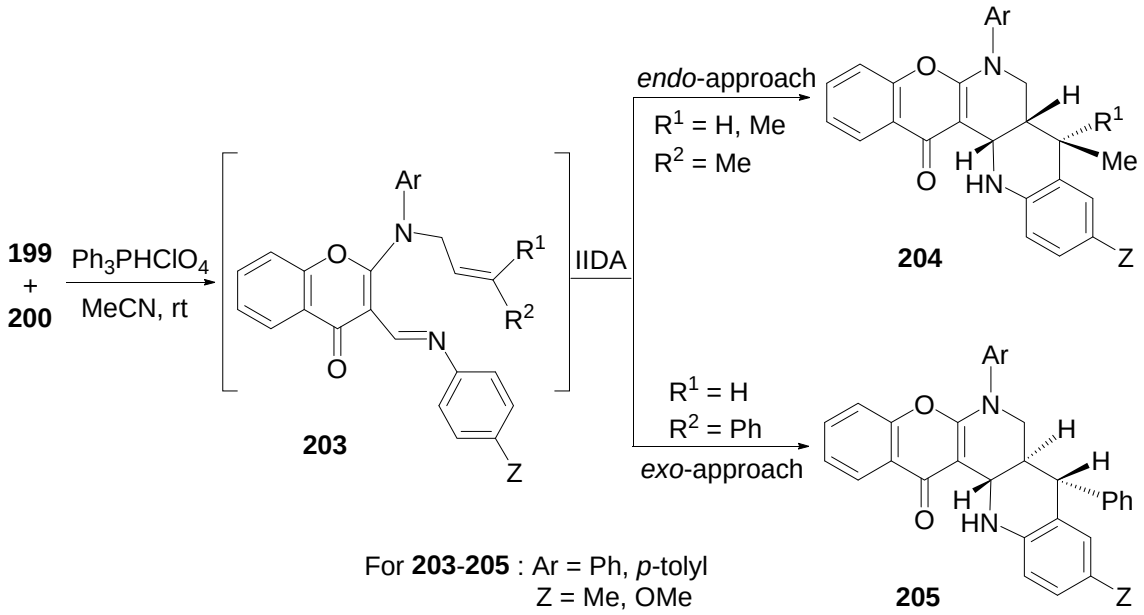


Scheme 21

9. Reactions of 2-(*N*-Alkenyl-*N*-arylamino)-3-formylchromones

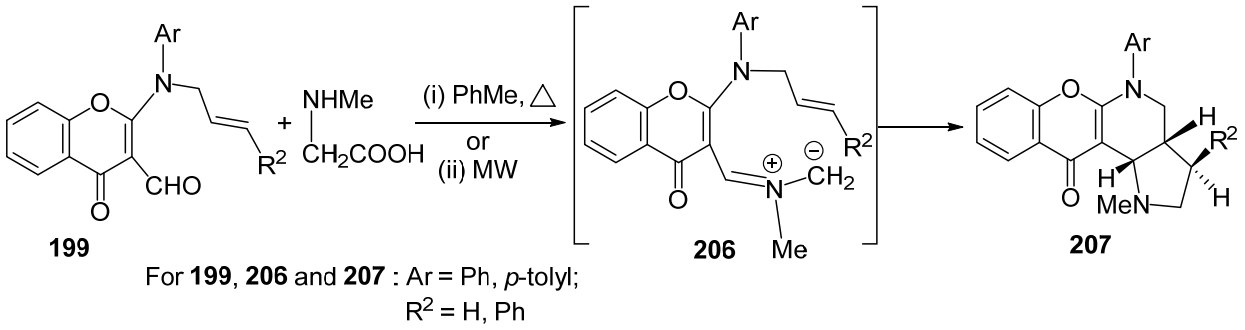
The chromone **3b** (≡ **199**), obtained by alkylation of **2b** (Ar = Ph, *p*-tolyl) with an appropriate allyl bromide, on treatment with the amine **200** in MeCN at ambient temperature gives a mixture of the amine exchange product **201** and the corresponding aldimine in its tautomeric form **202**, a small amount of **3b** remaining unreacted. The same reaction under Lewis acid ($FeCl_3$, $BF_3.Et_2O$ or $InCl_3$) catalysis affords either of the chromenonaphthyridines **204** and **205** (Scheme 22) in poor to moderate yield, the Brønsted acid triphenylphosphonium perchlorate (TPP) (40 mol%) giving the best results.[85] The aldimine **203** initially formed by acid catalyzed condensation of **199** with **200** undergoes intramolecular imino-Diels-Alder reaction (IIDA) (Povarov reaction); *endo*-approach of the dienophile part in **203** is favoured when R^2 = Me to form **204** whereas favourable *exo*-approach of that in **203** (R^2 = Ph) leads to the *trans* fused product **205**.





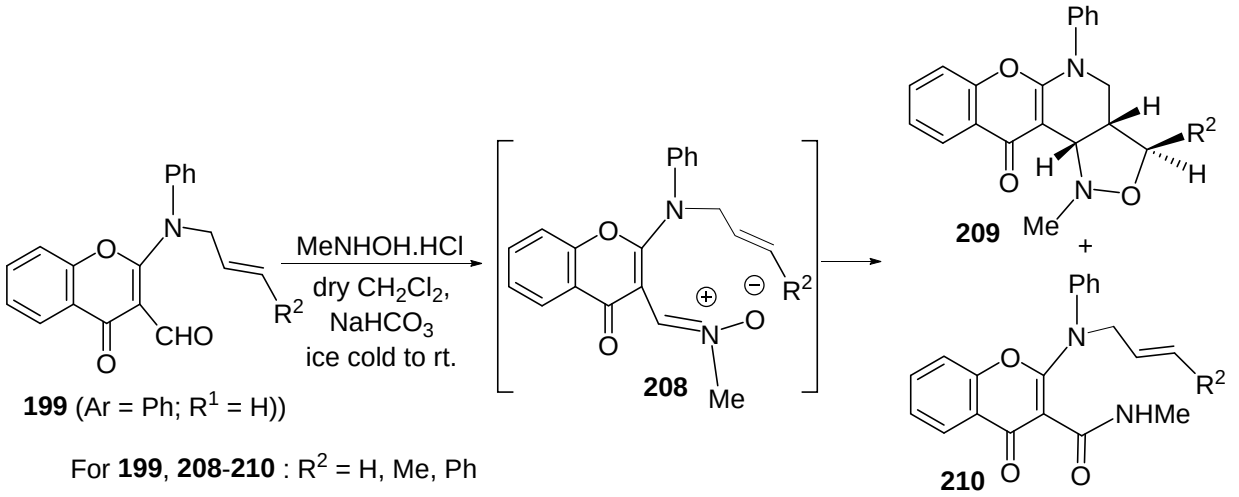
Scheme 22

When an equimolar mixture of the chromone **199** (R^1 = H) and sarcosine is subjected to conventional heating in toluene or microwave irradiation, the resultant azomethine ylid intermediate **206** undergoes regio- and stereo-selective intramolecular [3+2]cycloaddition giving the pyrrolo[2,3-*a*]azaxanthone **207** in good yields (Scheme 23).[86]



Scheme 23

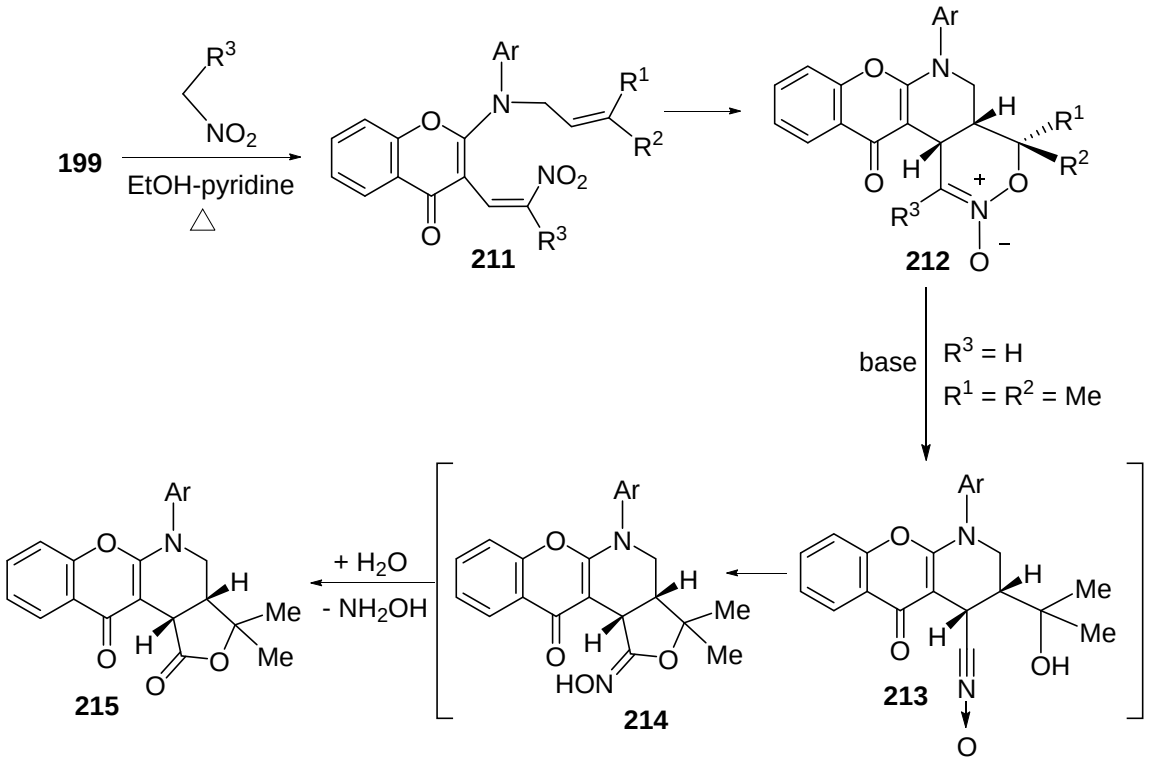
Regio- and stereo-selective intramolecular [3+2]cycloaddition of the nitrone **208** generated *in situ* from the chromone **199** (Ar = Ph; R^1 = H) and *N*-methylhydroxyamine leads to the chromenopyridine fused isoxazole **209** (80-90%), sometimes associated with the amide **210** as a minor product (Scheme 24).[87,88]



Scheme 24

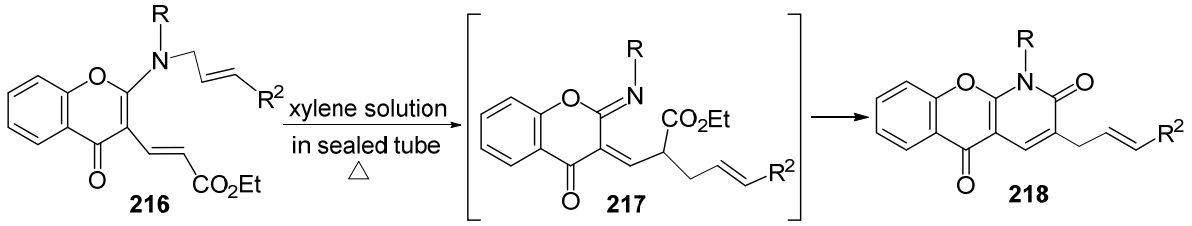
Base catalyzed condensation of **199** with nitroalkane $R^3CH_2NO_2$ gives the nitroalkene **211**. The compounds **211** (R^1 = R^3 = H; R^2 = H, Me, Ph) are stable and fail to undergo [4+2]nitroalkene – olefin cycloaddition whereas other Henry condensation products **211** (R^1 = H, Me; R^2 = Me, Ph; R^3 = PhCO, CO_2Et) undergo intramolecular hetero-Diels-Alder reaction to afford the polycyclic nitronates **212**. The nitronates **212** (R^3 = H) undergo further transformations in the presence of a base. For example, **212** (R^1 = R^2 = Me; R^3 = H) is not stable, but via **213** and **214** is transformed into the fused furanone **215** (Scheme 25).[89]

Wittig reaction of its aldehyde function with ethyl (triphenylphosphoranylidene)acetate converts the aminochromone **199** (R in place of Ar; R^1 = H) into the benzopyran-3-ylacrylic ester **216**. This ester **216** when dissolved in xylene and the solution heated in sealed tube at 220-230 °C undergoes a [1,5]allyl shift, the intermediate **217** cyclizing to the chromenopyridine **218**, migration of phenyl or benzyl group in **216** being completely ruled out (Scheme 26).[68] The fused pyridone **218** (R = Ph, R^2 = H) and its 8-chloro- and 8-fluoro- analogues have been evaluated *in vitro* for the cytotoxicity activity against various human cancer cell lines.[90]



R^3 = H, COPh, CO_2Et; Ar = C_6H_5, C_6H_4Me-*p*

Scheme 25

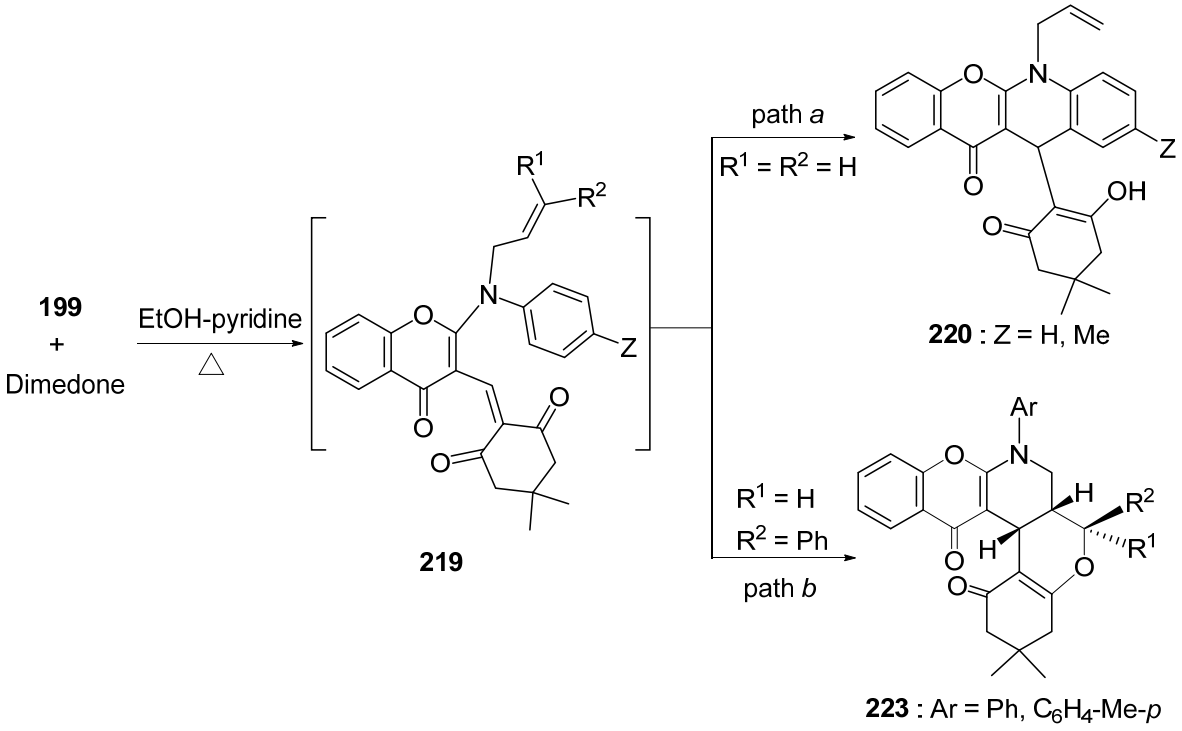


For **216-218** : R = Ph, $PhCH_2$; R^2 = H, Me, Ph

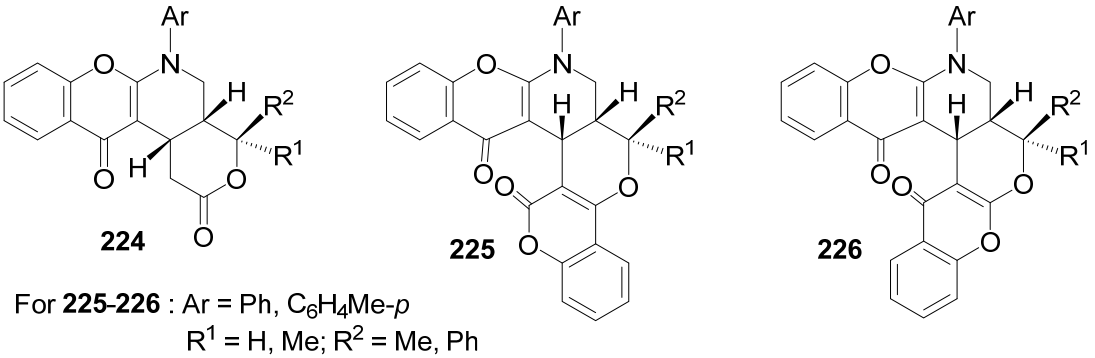
Scheme 26

The aminochromone **199** with active methylene compounds such as dimedone, Meldrum's acid and 4-hydroxycoumarin in refluxing ethanol-pyridine initially gives the non-isolable Knoevenagel condensates, the nature of the substituents on *N*-atom of its amino group determining the subsequent reaction courses. A competitive reaction between intramolecular Michael-type reaction (phenyl group functioning as nucleophile) and intramolecular hetero Diels-Alder reaction has been controlled by regulating the substituents on the N atom as well as on the dienophile unit.[91] Thus, the condensate **219** obtained from **199** and dimedone having

terminal alkene cyclizes to the benzopyranoquinoline **220** (Scheme 27 – path *a*) but that with a non-terminal alkene undergoes intramolecular hetero-Diels-Alder reaction with *endo*-approach of the olefinic moiety yielding the *cis*-fused product **223** (path *b*). It is worth mentioning here that **223** (R^1 = R^2 = H; Me or Et in place of Ar) also arises by base catalyzed reaction of 2-(*N*-methyl or ethyl-*N*-allylamino)-3-formylchromone **199** (R^1 = R^2 = H; Me or Et in place of Ar) with dimedone. The chromone **199** having non-terminal alkene on its amino nitrogen gives the tetracycle **224** with Meldrum's acid and a mixture of hexacycles **225** and **226** with 4-hydroxycoumarin.[91]



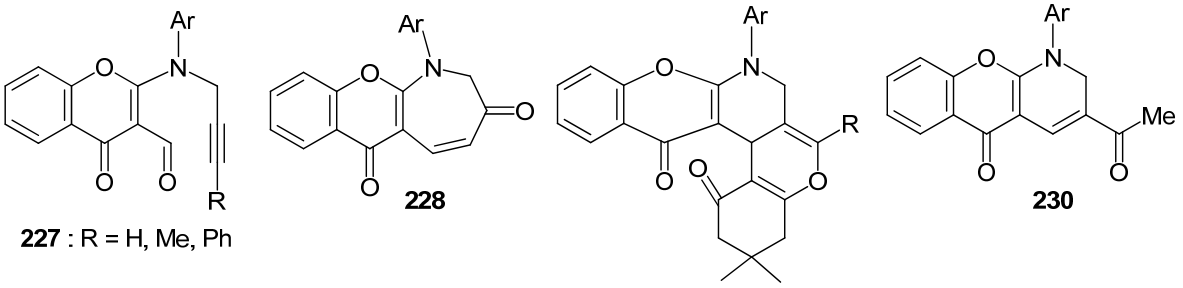
Scheme 27



10. Reactions of 2-(*N*-Alkynyl-*N*-arylamino)-3-formylchromones

Treatment of the aminochromone **2b** with Br-CH_2-C≡C-R in refluxing acetonitrile containing K_2CO_3 and NaI under an argon atmosphere gives 2-(*N*-alkynyl-*N*-arylamino)-3-formylchromone **3c** (≡ **227**). The chromone **227** (R = H) undergoes I_2-CuI (I_2 – 1 equiv., CuI – 0.2 equiv. stirring in MeCN at ambient temperature under argon atmosphere) mediated intramolecular alkyne – carbonyl metathesis (ACM) reaction yielding the chromeno[2,3-*b*]azepin-3,6-dione **228**; the chromone **227** (R = Me) fails to undergo ACM reaction.[92]

Microwave irradiation of a well ground equimolar mixture of **227** (R = Me, Ph) and dimedone undergoes domino Knoevenagel – hetero-Diels-Alder (DKHDA) reaction furnishing pyrano-azaxanthone **229** whereas conventional heating of **227** (R = Me) admixed with dimedone in ethanol-pyridine causes its ACM to the acylazaxanthone **230**.[93]



11. Conclusion

Syntheses of all the members **1-4** belonging to the 2-amino-3-formyl-1-benzopyran-4-one family, and their reactions with various nucleophiles and electrophiles, published to March 2016 have been comprehended.

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